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13. ABSTRACT *(Maximum 200 words)*

The Center for Innovative Minimally Invasive Therapy (CIMIT), is a consortium of nonprofit Massachusetts-based institutions led by Massachusetts General Hospital and includes Brigham and Women's Hospital, Massachusetts Institute of Technology and Draper Laboratory. The primary aim of the Center is to develop technologies that will advance the capability of modern medicine to diagnose and treat patients using minimally invasive and less costly approaches. CIMIT will coordinate and implement research programs in cardiovascular disease, cancer, stroke, trauma and critical care, that are supported by basic science and engineering development in biomaterials, endoscopic tools, energy delivery, intelligent decision systems, medical imaging, micro-sensors, outcomes, robotics and simulation. A unique military/civilian partnership fostered by CIMIT will allow DOD technologies to be evaluated by CIMIT investigators and facilitate the transfer to the military of successful minimally invasive approaches developed at CIMIT. An educational program, which includes coursework, seminars, and on site training opportunities, will serve the shared needs of academic and military physicians and scientists. The overall goal of CIMIT is to create a national program that combines clinical and technological excellence in order to generate, develop, and reduce-to-practice innovative and high-impact concepts in minimally invasive therapy.

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Table of Contents

CENTER FOR INNOVATIVE MINIMALLY INVASIVE THERAPY

Annual Report - October 1, 1998 - September 30, 1999

1.0 INTRODUCTION

The goal of the Center for Innovative Minimally Invasive Therapy (CIMIT) is to integrate clinical and technological excellence in order to generate, develop and rapidly reduce to practice innovative and high impact concepts in minimally invasive therapy that improve the quality and lower the cost of health care delivery. CIMIT enables researchers to explore, devise and implement new technologies, while providing real breakthroughs in research through the collaboration of academic medical centers, industry and the military. Significant progress has been made. In this first year, CIMIT has:

- Developed expertise and infrastructure to support key clinical focus areas and advanced technology teams.
- Revised the Advanced Technology Teams (ATTs) structure to reflect program needs and priorities.
- Initiated a collaborative research program in minimally invasive fetal surgery at the Children's Hospital of Philadelphia.
- Evolved isolated projects into programs in the Stroke and Critical Care Clinical Focus Areas (CFAs).
- Expanded the original technology assessment and outcomes ATT into its own program.
- Established a forum for fifty investigators, students and representatives from industry to meet weekly to share knowledge, results and challenges.
- Initiated collaborative research programs with DOD.
- Funded an academic site (Harvey Mudd College) as a first step in establishing a national CIMIT program.

As the Clinical Focus Areas and related research have gained focus, it becomes clear that developing individual projects into programmatic efforts derives greatest benefit. Stroke and Critical Care are the first areas targeted for this transition. The programmatic approach offers the opportunity to:

- Assess the value of each new technology or approach through similar methodology and to provide opportunities to compare and contrast values of each separately and in combination.
- Coordinate research for translation into clinical practice.
- Increase awareness regarding use and value of new technology; work across the health care system to speed the actualization of new technology into the fabric of delivery systems.
- Share scientific knowledge, results and challenges, relationships with industry and develop a focus for future research.

2.0 CLINICAL FOCUS AREAS

2.1 CARDIOVASCULAR DISEASE CLINICAL FOCUS AREA

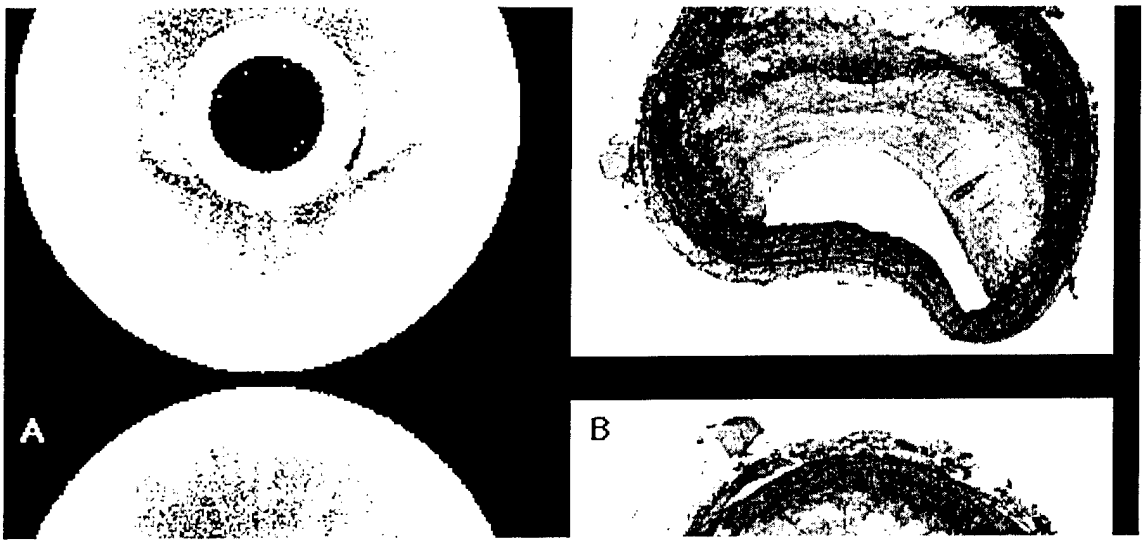
During the Q4 period, Dr. James Muller and Dr. Andrew Selwyn were designated as Co-Directors of the Cardiovascular Disease Clinical Focus Area. Both have extensive experience in clinical cardiology research and the application of technology to cardiovascular problems. There are 3 active projects in the area: the OCT project, the anastomosis project, and the vascular biology project.

Task 1: Detection of Vulnerable Plaque using Optical Coherence Tomography

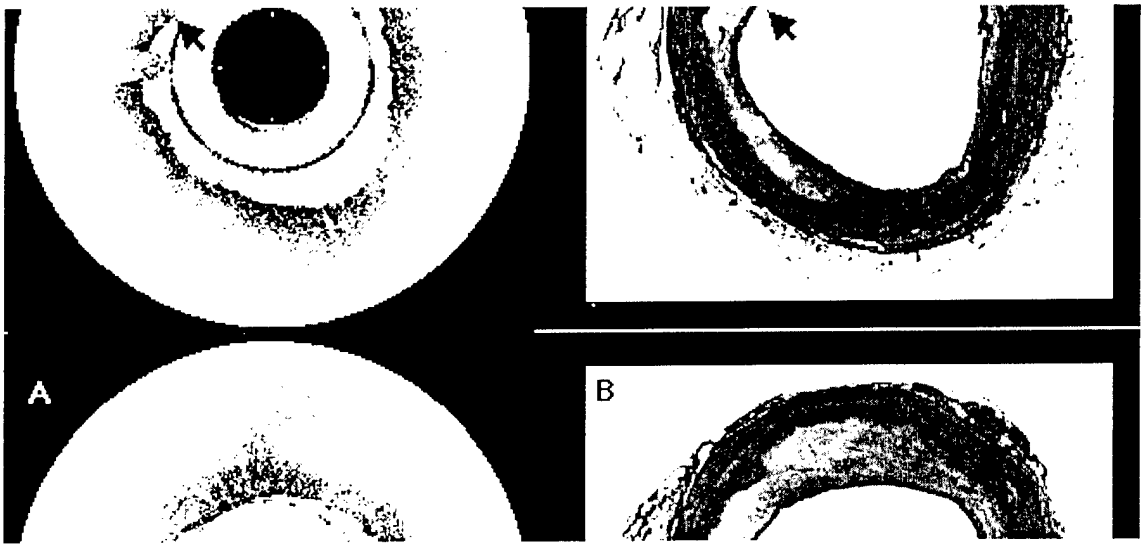
Specific Aim: The overall goal of this research is to develop, optimize and apply optical coherence tomography (OCT) for the detection of vulnerable atherosclerotic plaques in human coronary arteries. The task for year one is to develop the OCT catheter system, to demonstrate ex vivo that OCT can identify morphologic features that distinguish vulnerable from stable plaques and to determine catheter and imaging characteristics in a porcine model in vivo. If successful, we will extend the research to patients in the second year.

Progress: We have developed a 3 F and 7 F catheter-based OCT system for imaging vessel segments ex vivo. Over 60 segments have been imaged and correlated with histology. Architectural morphologic features have been identified in the OCT images, such as the intima, media, adventitia, internal elastic lamina, and external elastic lamina. In atherosclerotic lesions, lipid pools were identified in the OCT images and fibrous cap thicknesses were measured by OCT (30 - 450 μm). The correlation between OCT and histology was high for measured cap thicknesses ($r = 0.98$). An abstract has been submitted to the American College of Cardiology meeting describing our results. A 3 F OCT catheter has been constructed for in vivo swine studies and eventual human use. The device is constructed from a modified 3 F intravascular ultrasound catheter and is undergoing extensive testing prior to initiation of the in vivo porcine study.

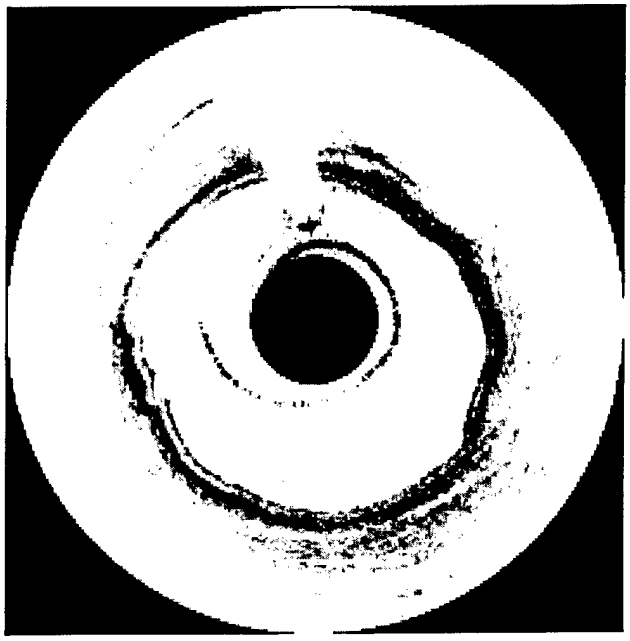
Plan: Our immediate research priorities are the initiation of the porcine study to test OCT imaging in vivo. This study will use the 3 F catheter to image coronary arteries in 5 pigs. Data obtained from this study will allow optimization of the imaging technique and the catheter for eventual human use. We also intend to continue the ex vivo work using OCT to image cadaveric coronary arteries. The data obtained from these experiments will enhance our database of OCT characteristics of coronary pathology



In vitro OCT image of a thick-walled coronary atheromatous plaque. Note the loss of the normal layered structure within the plaque. B. Corresponding histology.



In vitro OCT image of a vulnerable, thin walled plaque. Corresponding histology (arrows mark thin fibrous plaque wall).



In vivo OCT image of a swine coronary artery. The intima, media, and adventitia are clearly identified as discrete layers within the image.

In vivo OCT image of a stent deployed in a swine coronary artery. Shadowing of the metallic stent is seen as areas of lost signal in the OCT image.

Task 2: "Smart" Catheters

Specific Aim 1: Design catheters, which monitor the vessel wall during use and thereby improve safety and success of angioplasty.

Progress: The CIMIT Scientific Management Committee has decided not to fund this project in year one.

Task 3: Vascular Stent-Grafts

Specific Aim 1: Develop novel procedures for the treatment of aneurysms and vascular trauma using percutaneous placement of vascular stentn-grefts.

Progress: The CIMIT Scientific Management Committee has decided not to fund this project in year one.

Task 4: Minimally Invasive Cardiac Surgery — Endoscopic Coronary Anastomosis

The objective of this project is to optimize endoscopic approaches for minimally invasive coronary artery bypass graft surgery. We plan to develop a method for achieving video assisted, endoscopic coronary anastomoses in laboratory animals to pave the way for clinical application in patients with coronary artery disease. The specific aims are to:

Specific Aim 1: Evaluate the effectiveness and optimal technique for use of a tissue sealant as an anastomotic adjunct.

Background: Among an array of potentially useful synthetic hemostatic agents under development, a polyethylene glycol based hydrogel, FocalSeal ™, has some unique properties. Previous investigation in our laboratory supports that this sealant acutely prevents bleeding in arterial puncture wounds up to 2.8 mm, without associated tissue toxicity when applied to coronary anastomoses in chronic studies. One particularly interesting application may be as an external stent to maintain or increase the diameter of blood vessels. However, the sealant absorbs water as it polymerizes and swells *in vitro* up to 50-70 % in 24 hours. Depending on the mechanical effect, this might cause compression of the vessel lumen when used around the circumference of the vessel.

Progress: In twelve rats, we isolated the abdominal aorta from surrounding tissues and applied the sealant around the circumference of the vessel. After priming the surface to be treated with a photosensitive bonding agent, the sealant is applied from a syringe as a viscous liquid and then transformed to a solid gel with 40-second exposure to a blue-green xenon light. By applying gentle upward pressure on proximal and distal sutures that encircle the aorta, blood flow was temporarily stopped in the vessel during sealant application. An identical procedure, except for the application of sealant, was carried out in five control animals. All animals were allowed to recover from anesthesia, and re-assessed 24 hours later. Using Doppler ultrasound we measured the aorta's inner diameter and blood flow, before, immediately following sealant application, and 24 hours later. The aortic dimensions are recorded with a linear diagonal array probe, directly at the sealant application site (referred to as "central"), as well as, proximal and distal from the application site. Flow was 9.8 $\pm$4.0 pre sealant, and 9.5 $\pm$2.4 24 hours post sealant.

Conclusion: The data demonstrate no statistically significant decrease in the blood flow or vessel diameter 24 hours following sealant application in the experimental verses the control groups. We conclude that the hydrophilic hydrogel appears to exert no mechanical compressive effects on the vessel walls 24 hours after application. This supports our plans to utilize this gel in the anastomosis to coronary vessels.

Plan: Prepare manuscript for peer review. We plan further characterization of FocalSeal ™ surgical sealant as a hemostatic adjunct.

Specific Aim 2: Perform acute and chronic evaluation of a new micro-anastomotic device on coronary arteries.

Progress: We have used the Focalseal ™ tissue sealant in animal studies to determine its effectiveness in preventing bleeding and to see whether late scar formation would limit its usefulness in coronary surgery. The sealant successfully prevented bleeding in heparinized animals (with arterial puncture sites as large as 2.5 mm in diameter) and caused no noticeable scarring or anastomotic compromise in a study of dogs with coronary bypass grafts allowed to recover for three months.

We have performed the first half of the studies using the surgical sealant in the rat aorta. The histology is pending but the 24 hour recovery studies suggest that although the gel does swell rather markedly in vivo, it does not appear to compress the lumen of the vessel but may actually serve to stretch it open by expanding in an outward direction only. We are currently engaged in the study of different suture materials without any results yet.

Plan: When a vessel is encircled with a confluent layer of gel, it is unclear whether this expansion produces compression of the lumen. We plan to further investigate this question in a small animal model, by measuring flow and lumen diameter acutely and 24 hours after circumferential application of the sealant to the rat abdominal aorta. The second question that arose in our studies was the influence of the suture material and technique on bleeding from sutured anastomoses. When monofilament sutures are contained within a layer of sealant we have observed the "tail" of the suture acting in the manner of a wick to allow blood to escape the gel. Conceivably, a running suture line with minimal tails or a multifilament suture that allows the gel to penetrate will limit bleeding in sutured anastomoses.

Specific Aim 3: Development of a method for video-endoscopic coronary anastomosis.

Progress: We have now implemented the Computer Motion robotics system. The recent equipment acquisition and our surgical team's training on this system plus the Zeus robotic system has permitted us to start our canine studies. We feel strongly that this interface will make significant contributions to the goal of this project.

Plan: As we complete our training on the robotic interface, we will continue the canine studies to create video-endoscopic coronary anastomosis.

Specific Aim 4: Perform closed chest coronary anastomoses on an arrested heart.

Progress: The group has now done a total of eight canine closed chest coronary anastomoses on arrested hearts using the Computer motion robotics system, 3D visualization, heartport cannulae for instituting cardiopulmonary bypass and cardiac arrest and sealant as an anastomotic adjunct. The cases are very complex logistically and

efforts are in progress to improve the endoscopic system and robotic instruments. We are working with appropriate collaborators to perform these improvements.

Plan: We plan to further investigate this question in a small animal model, creating sutured anastomoses in the abdominal aorta of the heparinized rat to evaluate the severity of bleeding with the various techniques.

Task 5: Endothelial Activation Markers as Molecular Targets for Innovative, Minimally Invasive Diagnosis and Therapy in Cardiovascular Disease

The endothelial cells (EC) that comprise the lining of the cardiovascular system constitute a dynamically mutable interface in health and disease. In response to various inflammatory, thrombotic and atherogenic pathophysiologic stimuli, EC can undergo phenotypic modulation to a dysfunctional state that is marked by expression of "activation antigens", such as E-selectin (ELAM-1) and VCAM-1 (Athero-ELAM). The detection of soluble/shed forms of these cell surface markers in serum/plasma is already being utilized as a surrogate index of endothelial dysfunction in certain clinical studies. We propose to further exploit these EC phenotypic markers as molecular targets for innovative, minimally invasive diagnostic and therapeutic applications. Preliminary studies by our research group have demonstrated the feasibility of utilizing immunoconjugates (in the form of immunoliposomes), incorporating monoclonal antibodies to EC activation antigens, to discriminate between normal and cytokine-activated human EC in culture and to "home" to the activated EC lining of the aorta associated with early atherosclerotic lesions, following intravenous injection in experimental animals. Our initial strategy has been two-pronged.

Specific Aim 1: Development of robust models of endothelial activation in experimental animals (rodents - rabbits) for testing molecular targeting strategies. Note: all work involving rats in this overall project has been funded by sources other than the DoD.

Progress: Development of rat hind limb adenoviral injection model: For these experiments male Wistar rats with a minimum weight of 300 g are used since reproducible intra-arterial substance delivery can be achieved. Animals were anesthetized by intraperitoneal injection of 87 mg/kg ketamine and 13 mg/kg xylazine, which provided general anesthesia for about 60 min. The common femoral artery was canulated with a 29 G needle and 0.25% methylene blue diluted in heparinized saline was slowly injected allowing monitoring substance delivery by macroscopic staining of the hind limb. Under these conditions, volumes up to 500 µl could be injected into the femoral artery without any significant venous back flow or collateral arterial perfusion respectively.

Currently, we are testing: 1) whether an adenoviral preparation, RSV LacZ (which will mediates the expression of a bacterial enzyme, whose blue-colored reaction product is readily detectable, both grossly and microscopically), can efficiently infect the femoral artery and microvasculature of the hind limb, 2) what amount of virus is necessary (in pfu) and 3) kinetics a. How long does the virus need to stay in the vessels to achieve optimal infection? b. When, following infection, is the highest expression of the transduced genes observed? This will be optimized by determining the expression of the reporter gene product LacZ.

Plan: Male Wistar rats will be prepared for injection as described above, while the left hind limb will remain untouched and serve as a negative control. After clamping of the vein, three different virus dilutions (depending on the pfu titer) will be injected in a constant volume of 200 µl PBS. Three rats will be injected for each titer. In a first set of experiments, the vein will remain clamped for 25 min. to allow for efficient infection of the vasculature. (If this time is sufficient, it will be decreased, possibly to 5 min.) Rats will be allowed to survive up to three days after the procedure, and then sacrificed. The femoral arteries of both hind limbs will be prepared and stained for the presence of LacZ according to standard procedures. In order to determine the infection efficiency of the microvasculature, hind limb cross-sections will also be analyzed, while sections of the contralateral (uninjected) hind limb and also liver will serve as controls for non-target-geometry ("spill-over") expression.

Specific Aim 2: Explore feasibility of targeting endothelial activation antigens utilizing radiotracer immunoconjugates.

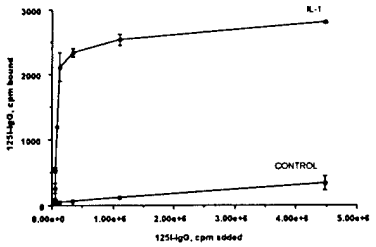
Progress: Construction of radiolabeled immunoconjugates: Two radiolabeling strategies will be applied for the visualization of E-selectin expression in the vasculature of our experimental animal models: direct labeling of monoclonal antibodies (mAbs) with ^{123}I (radioiodination) or by labeling mAb-DTPA conjugates with ^{111}In. Both methods should yield high specific activities of labeling and are suitable for external imaging purposes.

^{123}I label: The mouse monoclonal antibody H18/7 (intact immunoglobulin) which recognizes the extracellular domain of E-Selectin, or its corresponding Fab'_2 fragment, were labeled by Iodogen-mediated oxidation and purified by size-exclusion chromatography.

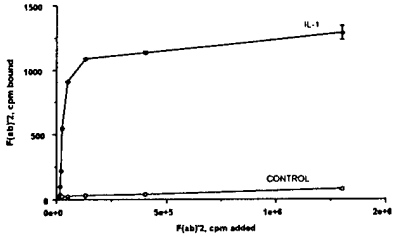
^{111}In label: Aliquots of an H18/7 preparation were dialyzed against four changes of BBS-buffer (10 mM sodium tetraborate, 150 mM NaCl, pH 8.5) at 4 °C before being reacted with a threefold molar excess of diethylenetriaminepentaacidic acid (DTPA) in DMSO for 1 h at room temperature. The DTPA-treatment was repeated and excess DTPA removed by extensive dialysis against CBS-buffer (20 mM sodium citrate, 150 mM NaCl, pH 6.5) overnight. Labeling with ^{111}In was achieved by directly adding $^{111}InCl_3$ (in 50 mM HCl) to the DTPA-antibody solution and incubating for 1.5 h at room temperature. Nonbound ^{111}In was removed by dialysis against PBS-buffer. An aliquot of the labeled antibody was used to determine the protein concentration in a BCA-assay. Labeling efficiency was subsequently determined as 4.7 µCi/µg protein.

In vitro testing of selective binding on cytokine-activated cultured human endothelial cells: Specific binding of the modified, labeled antibodies was tested as follows. E-Selectin expression on human endothelial cells (Ecs), seeded in 96 well plates was induced by incubating the cells in medium containing 10 u/ml recombinant human Il-1β for 4 h at 37 °C. Non-stimulated cells served as a control. The medium was removed and replaced by solutions containing HBSS/2.5% horse serum and various amounts of radiolabeled antibody (in case of ^{123}I label, fourfold dilutions starting from 550 nM were used; in case of ^{111}In label, dilutions ranging from 7.8 ng to 2 µg of total protein in a total volume of 100 µl were applied). In each case, the solutions were applied in triplicate to stimulated and non-stimulated cells. Incubation was for 45 min. on ice. The cells were washed three times with HBSS/2.5% horse serum before being incubated in trypsin

overnight at 37 °C. The trypsinized cells were collected and radioactivity counted in a γ-counter.

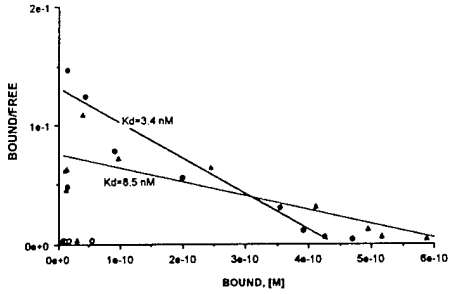


Binding of mAb H18/7 to Il-1 activated (closed symbols) and control cells (open symbols).



Binding of Fab2' H18/7 to Il-1 activated (closed symbols) and control cells (open symbols).

^{123}I label: Analysis of binding curves showed that labeled mAb and Fab'2 preserve high specificity for IL-1 activated cells. Approximately 10-fold more mAb and 20-fold more Fab'2 were associated with activated cells vs. control. Apparent binding constants were calculated using Scatchard analysis: 3.4 nM (mAb) and 8.5 nM (Fab'_2). Constant values suggest high-affinity binding of both whole antibody and the fragment with the surface of activated cells.



Scatchard analysis of antibody/Fab'2 binding to HUVEC.

^{111}In label: Results as summarized in Table I show that binding of as little as 30 ng of radiolabeled antibody to stimulated endothelial cells expressing E-Selectin on their surface can be detected while no binding is observed to non-stimulated cells. The results further imply that the labeling modifications do not alter the specific binding ability of H18/7.

Binding of ^{111}In-labeled H18/7 to stimulated and non-stimulated Ecs

^{111}In-H18/7 (total μg added)	**Ecs treated with IL-1β** (binding in [cpm] ± SD)	**Control Ecs (no treatment)** (binding in [cpm] ± SD)
2	24,915 ± 937	1,157 ± 35
0.5	17,233 ± 3,323	706 ± 51

0.125	10,103 ± 1,080	332 ± 23
0.0313	2,770 ± 171	211 ± 17
0.0078	958 ± 156	205 ± 8

Experimental procedure for ongoing studies: Having validated the use of these EC activation antigen-targeted radiolabeled immunoconjugates in a standard in vitro binding assay with inactivated and activated Ecs, we are now prepared to introduce them into the in vivo rodent hind limb model being developed under Specific Aim 1. For control purposes, preparations of a non-binding, class-matched "control" monoclonal antibody (i.e., one that does not react with activated or inactivated EC) will be prepared in parallel, and tested both in cultured Ecs, and also in vivo in the hind limb injection model, for nonbinding to the vasculature.

Plan: The next phase of the in vivo studies will have as its goal demonstration of activated-selective, geometrically localized, binding in the adenoviral-transfected rodent hind limb model. Initially this will be demonstrated using a combination of histochemical staining (LacZ) for the expressed EC antigen, and autoradiography on the same tissue sections for co-localization of radiolabeled antibody binding. Subsequent studies will then focus on the detection of this EC-activation-targeted, radio-immunoconjugate-labeled "signal" by external imaging techniques.

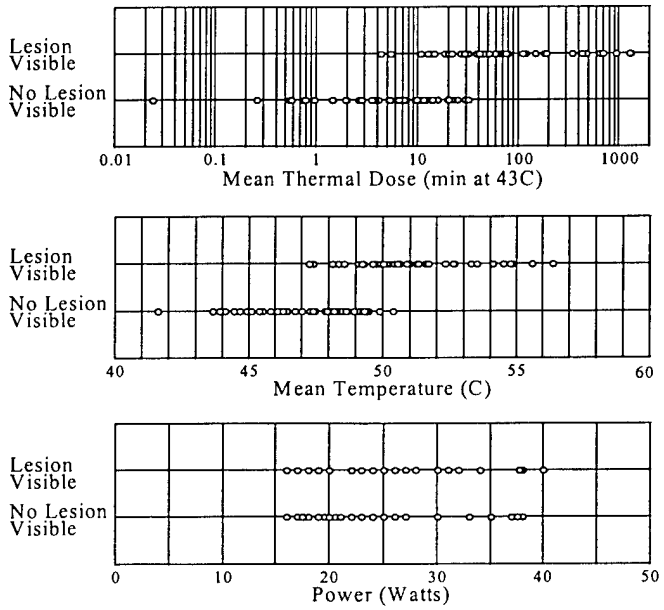
2.2 CANCER CLINICAL FOCUS AREA

Task 1: MRI-guided Focused Ultrasound Treatment of Breast Cancer

The overall hypothesis of this study proposed that focused ultrasound surgery guided by MRI can be used to noninvasively coagulate breast cancer tumors. Before this hypothesis could be tested in a clinical setting, all of the methods for the clinical protocol had to be developed and tested in animals. The ultimate goal is to evaluate the feasibility of inducing temperatures between 60 and 100°C in breast cancer tumor during 10-20 s sonication. The temperature elevations will be measured by using MRI.

Specific Aim 1: Develop treatment-planning procedures utilizing 3D-MRI information to determine the target volume and execute treatment. Note: all work involving animals in this overall project has been funded by sources other than the DoD.

Progress: Extensive animal experiments were performed to evaluate the accuracy of MRI to predict the temperature and thermal exposure threshold in animal tissues. In these experiments single sonications were performed while monitoring the temperature elevation in the rabbit tissue in vivo. The acoustic power was varied around the tissue damage threshold and then the tissue damage was evaluated using T2-weighted and T1-weighted contrast enhanced imaging. The MRI derived temperature and thermal dose were found to correlate well with the threshold whereas the power did not. The results are shown in the figure below. The result clearly shows that the MRI will allow the operator to assure that an adequate dose has been delivered in the target zone during single sonications.



The correlation between acoustic power, MRI derived temperature and dose to the tissue damage induced by ultrasound.

Specific Aim 2: Study the accuracy of MRI-derived temperature history for calculating the thermal exposure of tissue.

Progress: The MRI guided focused ultrasound system that was tested in our fibroadenoma study was slow and had system problems that caused the treatment times to be long. Since the breast cancer treatment will require a larger volume to be treated (margins around the tumor) the treatment duration was unacceptable. For these reasons we have been working with a company called TxSonoics who have installed a new focused ultrasound system in our magnet. We have been extensively testing this system to establish its reliability and safety for clinical treatments. In addition, we have performed a series of animal experiments that have shown that the volume treatments can be performed significantly faster with the new system. We have also established that complete target volume (similar to breast tumor volumes) coverage can be achieved in a clinically practical time by using multiple sonications. Our animal studies have also shown that MRI derived temperature maps can be used to measure the temperature elevation in each image voxel as a function of time. From this temperature history, the biological effectiveness can be calculated. The thermal exposure maps generated from serial MR images were shown to be good indicators of the effectiveness of the treatment. We have developed a computer program that performs all of the calculations during the sonications and displays the temperatures and the thermal exposures on-line. This program is critical for monitoring and control of the thermal exposures. The new sonication system and the temperature monitoring software is ready for clinical testing in the breast cancer trial proposed.

Plan: Our plan is to execute 14 breast cancer treatments with the MRI guided focused ultrasound system. The study design and plan will progress according to the clinical study protocol (IRB approved) submitted separately for DoD approval.

Specific Aim 3: Establish the thermal exposure required to assure complete tumor coagulation.

Progress: A study protocol that will evaluate the toxicity in the clinical setting has been developed. From our animal results, we have seen that MR imaging after the sonications is a very sensitive indicator of normal tissue damage. These imaging protocols will be used to evaluate the patients after the treatments with focused ultrasound surgery.

Task 2: Early Detection and Ablation of Epithelial Cancers

Subtask 1: ALA Enhanced Fluorescence Imaging of Barrett's Epithelium

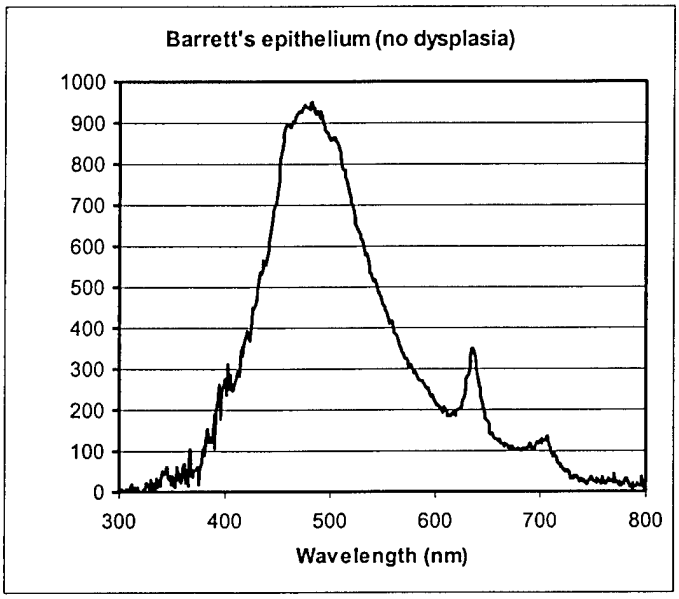
Specific Aim 1: Determine the accuracy of orally administered ALA for marking dysplasia occurring in Barrett's esophagus.

Progress: To date 17 patients have been enrolled in this trial. There are two study sties. The Massachusetts General Hospital is the primary study site and the Boston Veterans Administration Medical Center participates as a secondary study site. Eleven patients have been studied at the Massachusetts General Hospital and six patients have been studied at the Boston VA Medical Center. The mean peak PPIX fluorescence was significantly higher in Barrett's epithelium with high-grade dysplasia than in Barrett's epithelium without dysplasia. Thus, the preliminary results from this trial suggest that

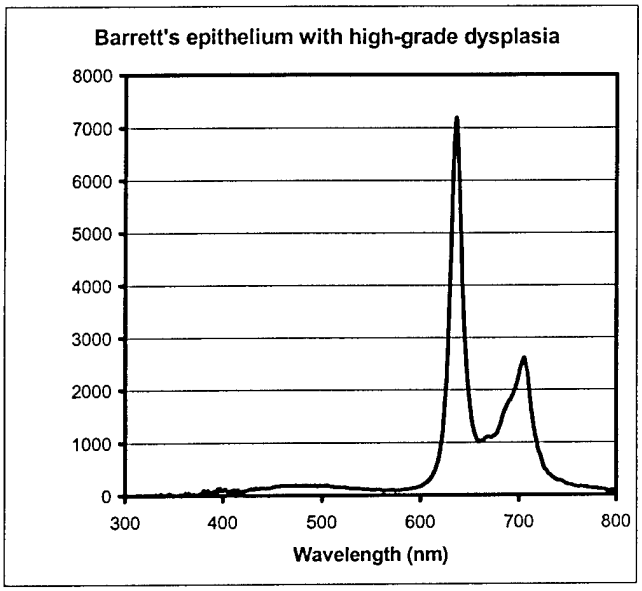
ALA-induced PPIX fluorescence appears to be a useful method of improving the detection of high-grade dysplasia in Barrett's esophagus.

A laser-induced fluorescence system was used to record fluorescence spectra from various sites within the esophagus during standard endoscopy. This system provides quantitative spectral information from sites where biopsies will be taken. Seventeen patients (15 males, 2 females) with Barrett's esophagus have been studied to date. Spectroscopic measurements were performed on 103 mucosal sites. Biopsies were taken from all mucosal sites where fluorescence measurements were made. The histopathological specimens were classified into one of 7 groups: invasive adenocarcinoma (2 sites), high-grade dysplasia (19 sites), low-grade dysplasia (12 sites), indefinite for dysplasia (13 sites), Barrett's metaplasia (18 sites), cardiac or gastric type mucosa (27 sites), squamous epithelium (12 sites).

Representative fluorescence spectra are shown below. The spectroscopically measured 635 nm peak PPIX fluorescence intensity was normalized to the intensity of a fluorescence standard (DCM, Exciton Inc., OH).



Typical spectroscopic curve of Barrett's epithelium without dysplasia (high autofluorescence peak at 450 nm, low PPIX fluorescence at 635 nm).



Typical spectroscopic curve of Barrett's epithelium with high-grade dysplasia (low autofluorescence peak at 450 nm) nm, high PPIX fluorescence peak at 635 nm)

The mean normalized PPIX fluorescence was significantly higher in Barrett's esophagus with high-grade dysplasia (0.33±0.17) than in Barrett's epithelium without dysplasia (0.09±0.01) and in normal gastric tissue (0.09±0.005). The data are summarized in the table below.

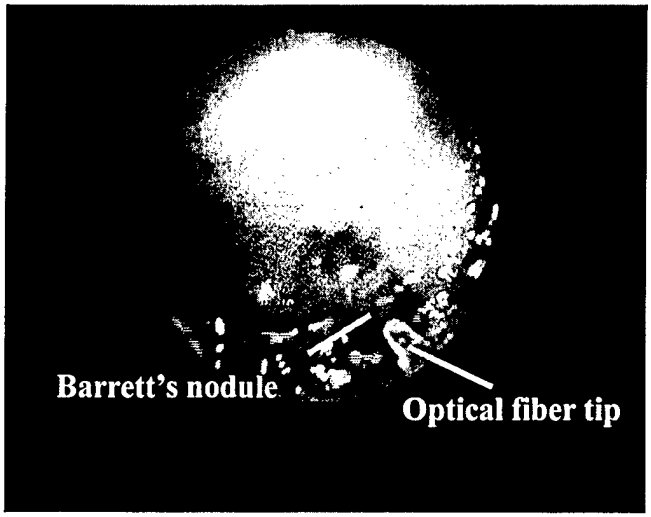
Tissue type	*Mean*	*Variance*	*p vs. HGD*	*Number of meas.*
Adenocarcinoma	0.14	0.02	0.26	2
High-grade dysplasia	0.33	0.17	-	19
Low-grade dysplasia	0.17	0.01	0.13	11
Indefinite for dysplasia	0.17	0.02	0.14	14
Barrett's (no dysplasia)	0.09	0.01	*0.02*	19
Gastric mucosa	0.09	0.005	*0.02*	27
Squamous epithelium	0.18	0.008	0.14	11

Note that the variance of the mean PPIX peak in high-grade dysplasia is high, since both very high and low PPIX levels have been found in HGD. Further studies will be required to investigate the origin of this high variability of PPIX level in HGD. Only one patient with adenocarcinoma has been seen in this study thus far. The low PPIX level in adenocarcinoma remains unclear, since only two spectroscopic measurements have been made on areas with adenocarcinoma.

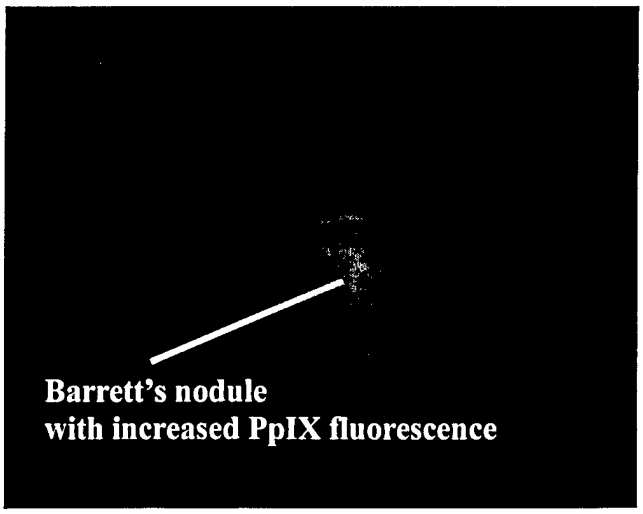
Specific Aim 2: Develop and test an endoscopic fluorescence imaging system for detecting ALA in the esophagus.

Progress: The image quality of the fluorescence imaging system and its specificity for detection of high-grade dysplasia have been improved by modifying the filter combination in the fluorescence system.

The quality of the fluorescence imaging system has been improved by modifying the filter combination in the fluorescence system. Sample images of a nodule with high-grade dysplasia as seen during white light endoscopy and fluorescence endoscopy are shown below. However, despite improvements in the optical filtering of the system, it is often difficult to differentiate between "true" bright spots (accumulated PPIX) and "false" bright spots, which are caused by light reflectance.



Barrett's nodule during white light endoscopy. The fluorescence probe is seen in the lower right corner.



The same Barrett's nodule in fluorescence endoscopy showing increased PPIX-fluorescence.

Subtask 2: OCT Imaging of Esophageal Lesions

The ultimate goal of this project is to determine the clinical utility of OCT for imaging lesions in the GI tract.

Specific Aim 1: Perform a pilot trial of OCT in unselected patients undergoing upper endoscopy to assess the spatial resolution and clinical usability of the present system.

Progress: The major focus of this OCT pilot trial was the OCT imaging of esophageal lesions, particularly patients with Barrett's esophagus and esophageal adenocarcinoma. In addition, patients with other gastrointestinal diseases have been studied (see table).

A total of ninety gastrointestinal subjects (75 upper endoscopies/15 colonoscopies) have been studied with OCT. Prior to 10/1/98 fifteen subjects were studied using Massachusetts General Hospital institutional funding. In these patients upper endoscopies including OCT imaging were performed. After 10/1/98 seventy-five subjects (60 upper endoscopies/15 colonoscopies) were studied using the OCT device. Biopsies were taken to compare the OCT images with the histopathological slides, and to create an OCT image atlas for normal and diseased gastrointestinal tissue. The analyzed tissue types (esophageal squamous epithelium, Barrett's mucosa, gastric type of tissue, esophageal adenocarcinoma) showed OCT features, which appear to permit accurate differentiation of these tissue types based on the OCT images alone.

Disease	*Number of cases studied*
Barrett's esophagus	43
Gastritis	13
Esophageal adenocarcinoma	8
Gastric adenocarcinoma	2
Esophageal varices	1
Gastric angiodysplasia	3
Colonic polyps	10
Other	10

OCT image criteria for normal esophageal squamous mucosa, for Barrett's epithelium and for gastric tissue have been established:

Normal Esophageal Mucosa: In all, 75 upper endoscopy images of the esophageal squamous mucosa have been taken. It was possible to clearly delineate five anatomic layers in the OCT images of normal esophagus acquired in vivo (see fig. 1). These layers represent epithelium, lamina propria, muscularis mucosae, submucosa, muscularis propria. These layers were distinguished by the relative difference in the intensity of their back reflection. In OCT images, an intense back reflection is denoted by a darker grey scale. Depth measurements performed on OCT images of cadaveric specimens and their corresponding histology were used to identify the layered structure visible in the OCT images (fig. 1). The close correspondence between the OCT measurements of the layer thickness and the histology measurements indicated that these layers could be clearly

identified and distinguished on OCT images of normal esophagus. The primary source of signal in OCT is scattering from structures on the size scale of the wavelength of light such as nuclei and other organelles within cells. Since these structures do not comprise a continuous, localized boundary at the junction between layers in tissue, interface artifacts are not present in OCT images. Mucus within the glandular cells was not highly reflective in the OCT image and gave the impression of roughly circular voids.

Barrett's Esophagus: Forty three patients with Barrett's esophagus have been studied using the OCT device. Barrett's mucosa is characterized in OCT by a loss of this layered architecture, an irregular mucosal surface and submucosal glands (see fig. 2). Glands can be recognized as either pockets of low reflectance below the epithelial surface of invaginations through the epithelium. While the reflectivity of the glands was similar to that of the stomach glandular epithelium, the configuration of glands was abnormal and disorganized. Observation of the lamina propria, muscularis mucosa and deeper structures was typically not possible due to the loss of signal or shadowing arising from strong scattering within the metaplastic epithelium. Barrett's esophagus with and without dysplasia has been studied with OCT. Although dysplasia is partly defined by subcellular features (e.g., nuclear size and shape, nuclear-to-cytoplasmic ratio) which are beyond the resolution of OCT resolution, in our OCT pilot trial, features of dysplastic Barrett's mucosa (e.g., irregular mucosal surface, irregular shaped glands) have been observed. A promising indicatior for detection of dysplasia in Barrett's esophagus by OCT. In addition, subcellular changes in dysplastic Barrett's mucosa like an increased nuclear-to-cytoplasmatic ratio, may alter the light reflection characteristics of Barrett's epithelium leading to an enhanced contrast in OCT images of Barrett's epithelium, an additional feature for the detection of dysplasia.

In several patients, Barrett's mucosa underneath squamous mucosa could be detected by OCT. This encouraging finding may lead to new treatment modalities for high-grade dysplasia in Barrett's esophagus (e.g., photodynamic therapy, electrocoagulation). Currently, an increase of squamous overgrowth over Barrett's mucosa cannot be visualized by conventional endoscopy or endoscopic ultrasound because of incomplete squamous reepithelization. Since sufficiently deep biopsies are often hard to obtain, surveillance of these areas in Barrett's patients is difficult and carries the risk of developing adenocarcinoma underneath normal squamous epithelium. OCT maybe very helpful in the detection of Barrett's epithelium underneath squamous mucosa.

Normal gastric tissue: OCT images of the gastric antrum acquired in vivo reflected marked morphological differences between glandular epithelium and squamous epithelium. Most significantly, the layered structure seen in OCT images of squamous epithelium was not observed. Instead, epithelial glands could be seen emanating from the surface of the epithelium. In areas of tissue that contained mucus, the OCT image was less reflective. Whereas, in the lamina propria, which contained more heterogeneous cellular and collagenous components, the reflectivity was stronger giving the surface epithelium a striated or stippled appearance. Also, the penetration depth of OCT images of the stomach (750 μm) appeared to be less than that of the esophagus.

Adenocarcinoma: Eight patients with esophageal adenocarcinoma and two patients with gastric adenocarcinoma have been examined with OCT. Typical OCT images of

esophageal adenocarcinoma showed a loss of normal tissue architecture and a very irregular tissue appearance. In gastric adenocarcinoma a loss of the normal "crypt-and-pit-architecture" has been seen. However, these data are too preliminary to assess if OCT can improve the staging (early stages) of cancer.

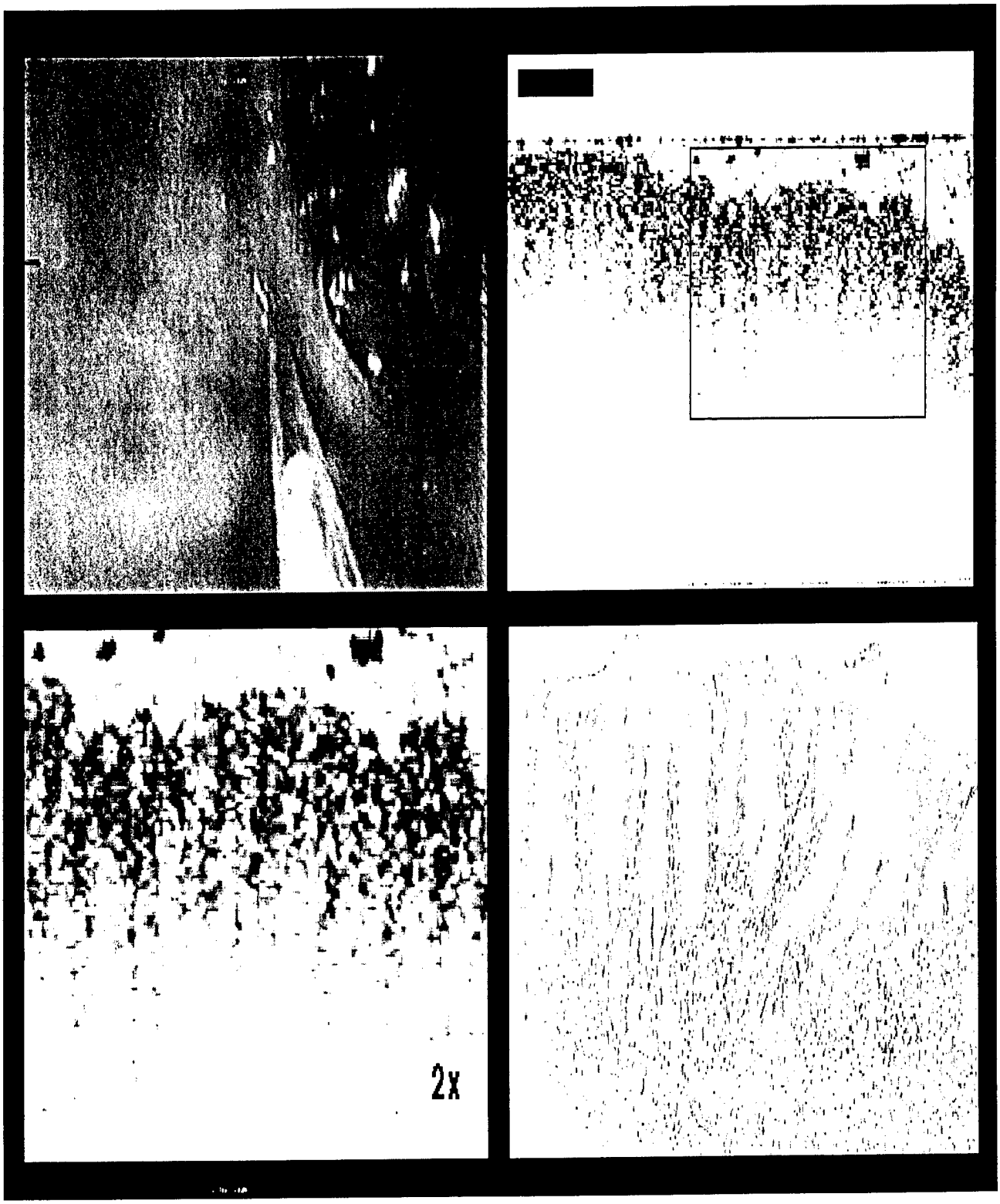
Specific Aim 2: Perform a direct comparison of OCT against 20 MHz ultrasound for imaging esophageal lesions.

Progress: An initial study of 20 MHz ultrasound in vivo and an in vitro sample showed its resolution and depth of penetration to be too inferior to OCT so that a direct comparison with OCT was felt to be meaningless. Thus, until an improved ultrasound devices become available, this portion of the study will proceed no further.

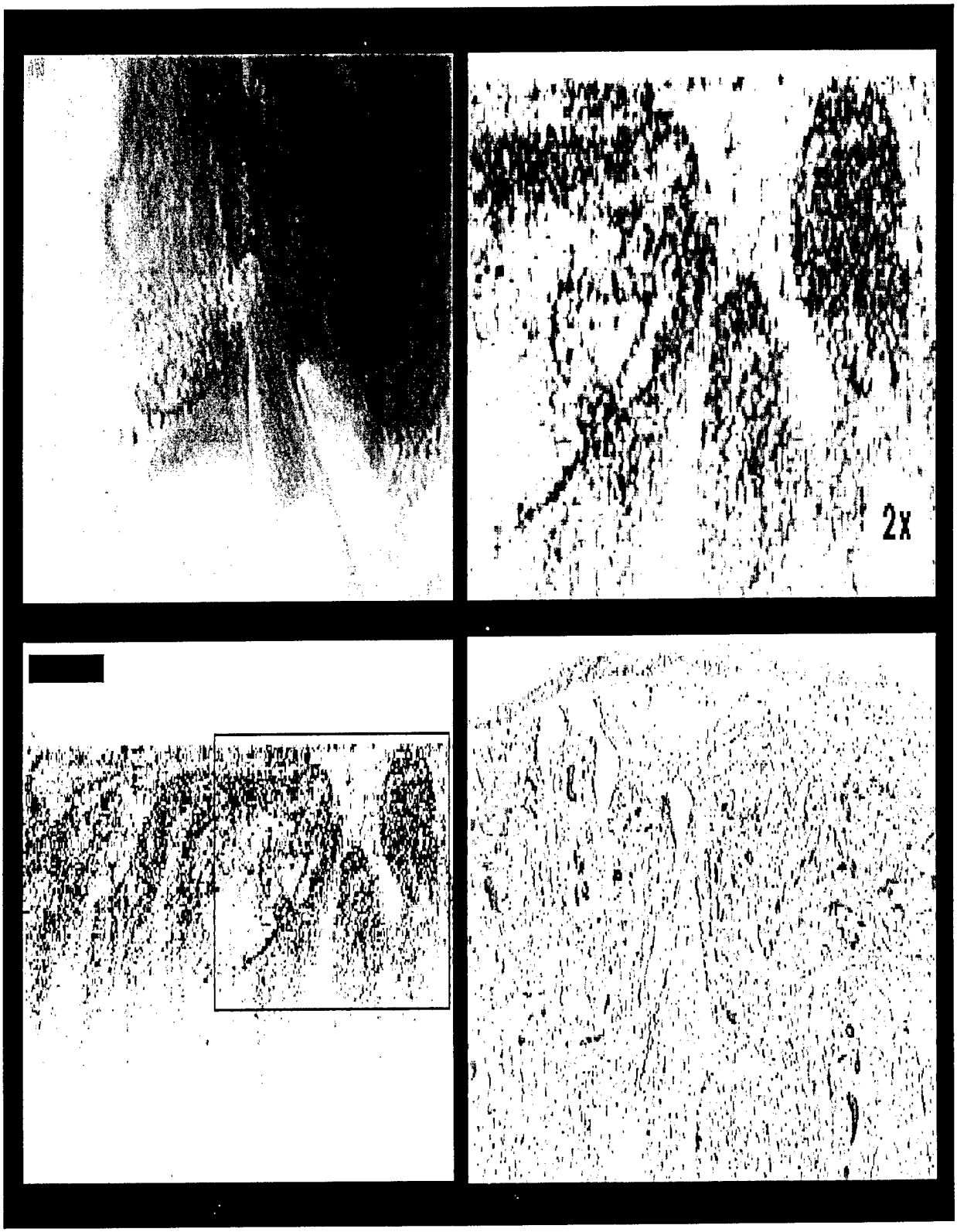
Specific Aim 3: Improve catheter design based upon the findings in Specific Aim 1 so that overall usability is improved and that it is possible to use the catheter with other endoscopes (e.g. colonoscopes, laparoscopes, etc.).

Progress: The overall usability of the catheter has been improved. Early catheter prototypes used a single layer plastic sheath to enclose the mechanical and optical components. This material was very transparent and sterilizable, but we found that when the catheter was placed in contact with the epithelium of the GI tract, the lumen of the sheath was distorted, constricting the mechanical core and inhibiting imaging. We have developed a bilayer sheath using plastic and nylon that provides both lower lumen distortion and lower friction between the sheath and the mechanical core. The new sheath greatly reduces the binding problem.

Additonally, a new catheter which may be used for sigmoidoscopies has been built. A total of 15 patients, with colonoscopies have been investigated with OCT. In 10 of these patients, colonic polyps have been found. Preliminary results suggest that OCT may be able to differentiate normal colonic tissue from colonic polyps. Further studies are necessary to determine if OCT can differentiate adenomatous polyps from non-adenomatous polyps.



Normal Gastric Tissue



Barrett's Esophagus

Plan: Next year we plan to 1) perform a clinical trial of OCT in different gastrointestinal diseases (gastritis, gastrointestinal neoplasias, colonic adenomas, esophageal varices) to define the clinical value of OCT in these diseases. A major focus of this trial will be the use of OCT in the lower GI tract, 2) perform a prospective blinded trial of OCT during endoscopy to establish sensitivity and specificity of OCT in the diagnosis of specialized intestinal metaplasia, and 3) develop a polarization sensitive fiber optic OCT system.

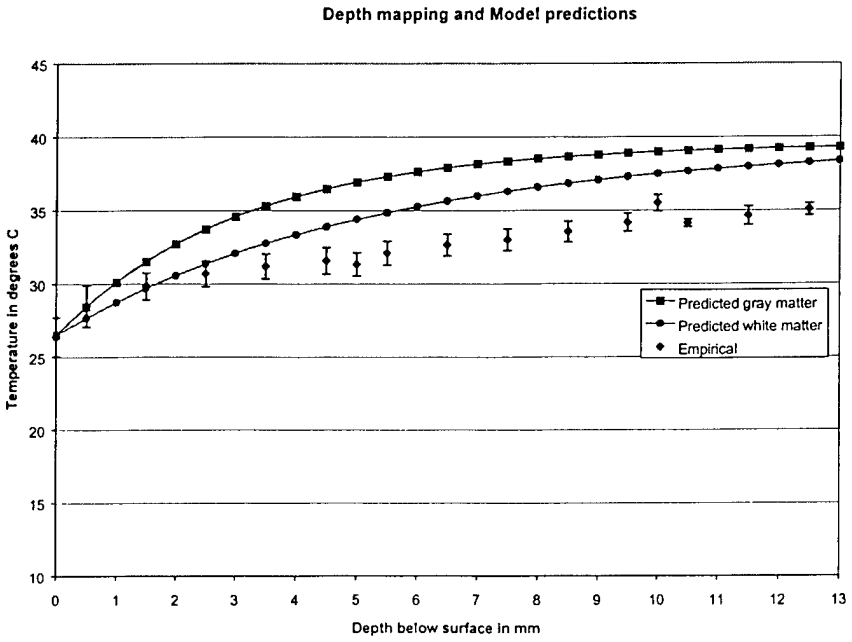
2.3 STROKE CLINICAL FOCUS AREA

Task 1: Acute Stroke Management – Neuro-Protection

Specific Aim 1: Develop a means to quickly cool the brain cortex to afford neuroprotection.

The primary aim of this project is to develop a means to limit the extent of damage resulting from brain infarction secondary to ischemic injury. Cerebral hypothermia has been shown to be the most potent neuroprotective strategy known. Its use as a neuroprotectant in ischemic brain injury is limited only by the lack of the means to achieve it in a rapid, safe fashion. The cerebral hypothermia project focuses on developing a method to selectively cool the surface of the cerebral cortex to achieve this goal.

Progress: In the first year of this project, the bioheat transfer problem of cortical surface brain cooling was modeled using a one-dimensional steady state equation as described by Pennes (original work done in 1948). Initial parameters for the model were estimated based on anticipated values for brain tissue temperatures during surface cooling. A cooling pad was developed to induce regional cerebral hypothermia on the cortical surface of the dog. When studies of cortical brain cooling *in vivo* were completed, additional empirical data became available and were fed into the bioheat transfer equation to obtain a more accurate model. Results from this refined model were then compared with measurements from *in vivo* depth mapping.



As can be seen from the graph above, the empirical measurements (expressed as mean $\pm$ SEM, n=4) suggest that brain cooling from the surface is achievable to a greater extent and at greater depths than was predicted by the mathematical model. The source of the

discrepancy perhaps lies in the model's limited assumption that brain tissue perfusion is uniform throughout the entire volume, when in fact, this is not the case. Cerebral blood flow moves in a centripetal direction from the surface cortical vessels to the deeper white matter regions of the brain. This provides the cooling device with a much greater cooling effect, since as it can cool blood prior to its entry into brain tissue. The model was run to produce two different curves, one for gray matter and one for white matter, because of the different perfusion values in these different brain tissues. The gray matter, which receives greater blood flow because of its higher inherent metabolic activity, will be more difficult to cool IF the blood with which it is perfused is at warm body temperatures. The heterogeneous composition of the *in vivo* animal brain alone, however, is clearly not able to completely explain the greater than expected cooling results, as the empirical measurements appear to exceed even the predicted cooling results in low-perfusion white matter.

The results of brain cooling in normal animals are very encouraging. It has been demonstrated *in vivo* that empirical measurements of regional cerebral hypothermia confirm the initial belief that regional brain cooling can be achieved with a cortical cooling device. Ongoing efforts to create reproducible cerebral infarctions will provide the study with an opportunity to test the effectiveness of this cooling strategy in reducing infarct size in animal models.

This work has resulted in the submission of an abstract to the American Association of Neurological Surgeons, April 2000 meeting in San Francisco, CA. A full paper is planned for submission to a peer review neurosurgical journal within the quarter. Patent disclosures for a prototypical surface cooling device are in preparation.

Plan: To demonstrate the ability to create a consistent focal stroke in the dog model; to investigate the effects of surface brain cooling on reducing infarct size; and to construct devices to examine the optimal means of noninvasively attaining access to the subdural/subarachnoid space in order to cool the brain surface.

Task 2: MRI Guided Rapid Laser Endovascular Photoacoustic Recanalization (LEPAR) for Hyperacute Stroke and Stroke Predictive Modeling

Determining whether a particular treatment strategy decreases the extent of brain injury in acute stroke patients is currently limited to assessing their level of function at 3 months after stroke. The number of variables other than the extent of brain injury which contribute to this metric make it an exceedingly clumsy tool with which to develop new stroke therapies. In contrast, early MR studies which assess perfusion and diffusion weighted imaging are strong predictors of final stroke size. A new technique (hypothermia, energy assisted thrombolysis) which protects the brain should favorable alter the predicted stroke damage based on the initial, pre-treatment assessment. To further define this means of assessing for neuro protection we have moved to a statistically powerful method which estimates the probability of viability vs. death of a large number of small brain regions in an individual patient.

Specific Aim 1: To demonstrate efficacy and tissue safety of the LEPAR device and to maximize patient safety by defining the irreversible brain injury probability by diffusion MRI in a primate model. Note: all work involving non-human primates and canines in this overall project has been funded by sources other than the DoD.

Over the past year, initial experiments in animals were designed to confirm the efficacy and tissue (vascular and brain parenchyma) safety of a laser based approach. Studies on non-human primates were designed to define the precision with which functional MR images of the brain define irreversible injury. Ultimately in stroke patients, a specially designed angiographic suite will be used which will include both state of the art MRI and digital subtraction angiographic instruments

Progress: MGH animal committee approval for the proposed studies was obtained. However, in deciding on a device to employ, the team chose to work with Endovasix. This company has already extensively tested their laser device in animals as well as in preliminary studies in humans. We now have IRB approval and a contract with Endovasix to perform a clinical trial in patients.

MGH animal safety committee and the DoD approval are in progress. The MGH animal committee raised concerns regarding the feasibility of the non-human primate model. Before the experiments proposed for this project (and another parallel project not funded by the DoD) would be considered, demonstration of the feasibility of the model was requested. Successful demonstration of the model in 2 non-human primates was accomplished without the use of CIMIT/DoD funds. Nonetheless, the experience and expertise developed in the course of demonstrating the model will directly benefit the achievement of Specific Aim 2.

The last quarter yielded additional positive animal data. Data regarding size analysis of the microembolic subcapillary particles created with laser induced cavitation of clot have been compiled. Also, a survival model to assess the potential risk of "downstream emboli" with the clot lysate has been created. The experimental model initially centered on fragmenting matured clot ex-vivo with Laser Endovascular Photo Acoustic Recanalization (LEPAR) and immediately injecting the newly fragmented mature clot into the carotid circulation through a standard angiographic catheter. Four canine samples were assessed for the creation of distal strokes. Additionally, one of the models was survived for 48 hours after anesthesia recovery and the model demonstrated a normal behavioral baseline with no evidence of any neurologic deficits. There were no strokes demonstrated in any of the four samples in spite of the injection of a large lysate burden. This experimental information has been submitted for consideration to the Stroke section meeting of the American Heart Association and to the Cerebrovascular Joint meeting of the American Association of Neurological Surgeons/ Congress of Neurological Surgeons/ American Society of Interventional and Therapeutic Neuroradiology.

The construction for the MRI Interventional suite has begun and is expected to be operational by the Spring of 2000. Timely approval from the MGH and DoD animal care committees for the non-human primate model for the research would enable the team to begin MRI guided rapid laser endovascular photoacoustic recanalization in hyperacute stroke patients in the Fall of 2000.

Plan: To refine the clinical techniques and methods used during employment of LEPAR.

Specific Aim 2: To develop novel methodologies for stroke predictive modeling.

Progress: Over the past year imaging data has been analyzed and re-analyzed from patients receiving a novel therapy, basic fibroblast growth factor (bFGF), and it was

found that the predictive model confirmed that the medication reduced infarct size from that predicted in a dose-dependent manner. This result which stems from the assessment of a large number of regions in any given individual treated or placebo patient was statistically significant (p=0.007) despite having only 7 subjects in the trial. A paper which details the model and a second paper describing the results in patients treated with bFGF have been submitted for publication.

Extensive time has also been spent working with data from new MRI machines and rewriting our programs for use with the new machines. These new machines are somewhat higher performing than previous instruments. These and other new instruments should allow the team to make marked improvements in diagnostic capabilities.

A patent disclosure for the predictive model of final infarct size based on the initial scan has been submitted.

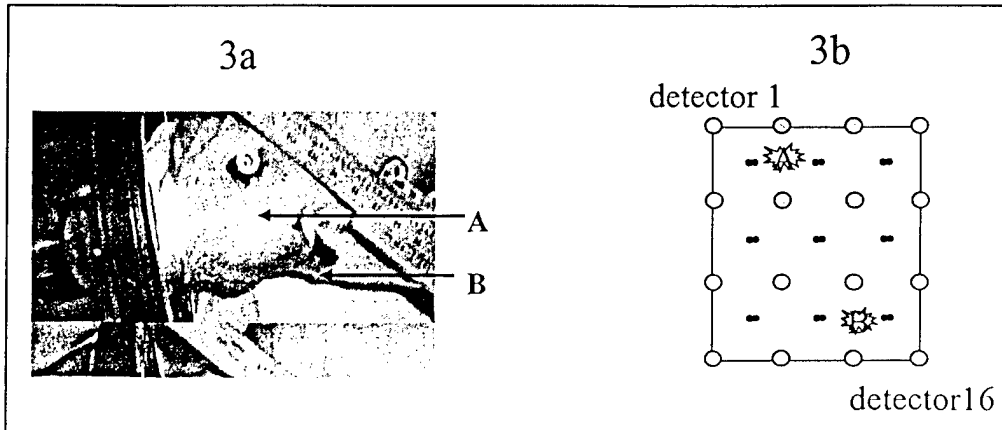
Plan: To test the model on larger numbers of acute stroke patients at various times from stroke onset to predict final infarct size and location based on acute MR data.

Task 3: Optical Monitoring and Imaging of Stroke

Stroke is the third leading cause of death in the U.S. and the leading cause of disability. Because of the risks associated with stroke treatment, an appropriate continuous-monitoring method is needed to guide treatment.

Specific Aim 1: Build the continuous-wave and frequency-domain diffuse optical tomography systems needed for testing the hypothesis in animal and clinical studies.

Progress : A 3rd generation continuous-wave (CW) system which features the ability to acquire 10 images per by frequency encoding of the spatial positions and different wavelengths of the source light so that they can be distinguished by each detector is under development with the assistance of a professional engineering firm, TechEn. Schematics and circuit diagrams have been prepared and modules of the system tested. The complete system with 18 sources and 16 detectors should be finished October, 1999 at which point testing of the system will begin. Successful testing of the system will lead to building of the final CW system that will allow 10 images per second but with unlimited numbers of sources and detectors.



Top view of bleed A and B on the piglet head (3a) , and their positions relative to the probe (3b)

Specific Aim 2: Validate the systems in animal models while at the same time 1) assessing sensitivity to and specificity for different inter-cranium bleeds 2) optimizing instrumentation and analysis algorithms and 3) developing experimental protocols for human subject studies.

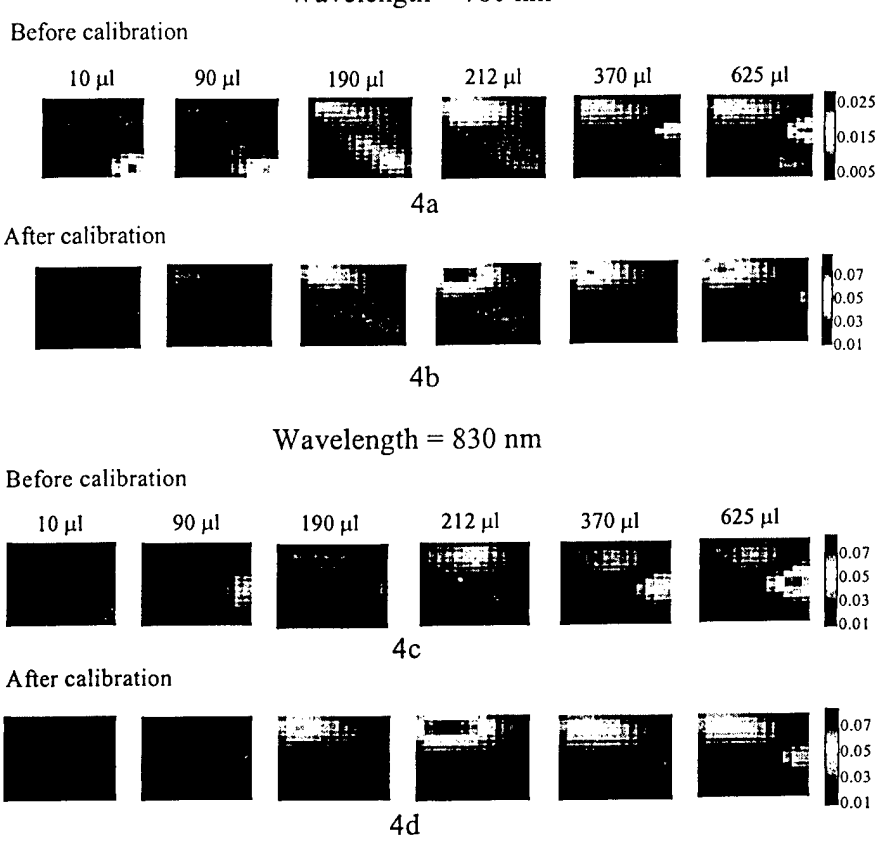


figure4. Time course images of bleed A at 780 nm , and 830 nm with and without applying the calibration approach

Progress: A piglet model was used in this study. The experimental set-up is a hybrid system of diffuse optical tomography and x-ray CT. Measurements were made on the bench of the x-ray scanner. A one-week old piglet, weight 3 kg, was sedated, intubated, and ventilated during the experiment. The femoral artery was catheterized for continuous blood pressure monitoring, fluid infusions, and blood extractions. The blood taken from the femoral artery was delivered through two small needles insert 2 cm through scalp, skull, and brain tissue with a separation of about 2 cm. The combined thickness of the scalp and skull is about 1 cm, so the blood was injected into the brain at a depth of about

1 cm. The injection speed was controlled by a step motor at a rate of 42 μl/minute. A total volume of 625μl of blood was injected for each bleed over 15 minutes. Images were reconstructed every 15 seconds. Bleed A was created first, then bleed B. The optical probe was placed on top of the piglet's head. The probe has 16 detectors and 9 sources at each of 780 nm and 830 nm. Before starting to inject blood into location A, a baseline was measured and used to find the coupling coefficient of each source-detector channel and also the background optical properties. The calculated absorption and effective scattering coefficients are 0.0672 cm^{-1}, 8.44 cm^{-1} at 780 nm and 0.0666 cm^{-1}, 7.61 cm^{-1} at 830 nm. This corresponds to a SO_2 of 58% and HbT of 78 μl/mol. The coupling coefficients were then used to normalize the raw detection data for image reconstruction. After bleed A was generated, another baseline was measured before injecting blood into location B. Right after the optical measurement, x-ray CT images were taken to identify the positions of the bleeds.

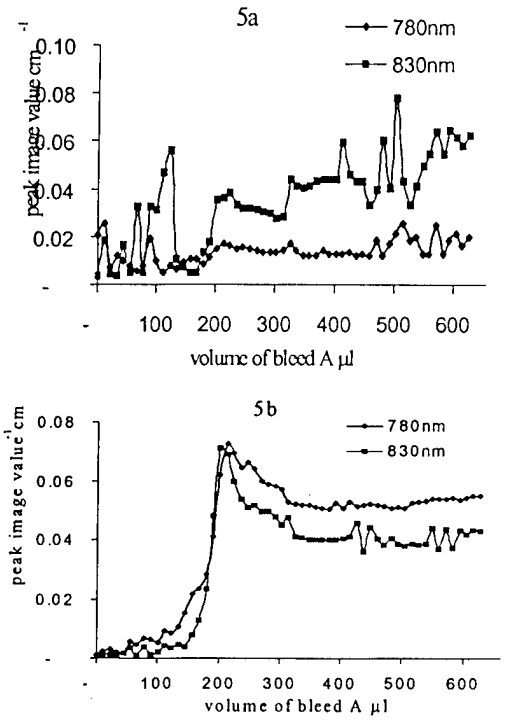
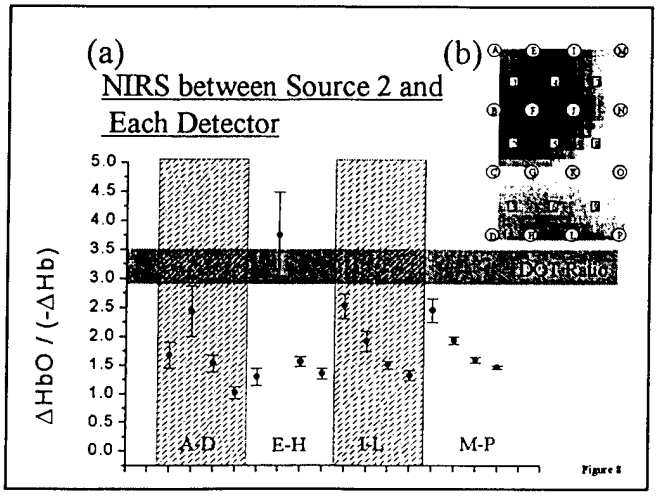


Image peak value vs the volume of bleed A without and with using the calibration approach

Figure shows the time course images of bleed A at both wavelengths. The 2D images are reconstructed using simultaneous iterative reconstruction technique (SIRT) and assuming that the piglet head is semi-infinite. It can be seen that the artifacts appeared in the figure are greatly reduced after the calibration procedure. The image amplitude is also different after the calibration.

Figure shows the time course plot of the peak image value of bleed A at the two wavelengths. Without calibration, the plot is very noisy, no clear build up of the bleed can be observed. This can be explained by the figures, which show that the amplitude of the artifacts are comparable or even larger than the real image values. After the calibration (b) we see clearly the development of the bleed A. The sensitivity of the DOT system to the bleeds is about 50 μl. The peak is somehow mysterious. It may be caused by the accumulation of the blood along the hole where catheter goes into the brain before the pressure is high enough for the blood to disperse deeper. The slope of the curve becomes smaller at the end because of the saturation effect of the detection. The blood injected later tends to go deeper and the detectors are less sensitive to it.



Specific Aim 3: Develop next generation image reconstruction algorithms by moving from 2D to 3D reconstructions that account for boundary conditions, image fusion of anatomical MRI and CT with optical specificity to improve overall image specificity.

Progress: Near infrared spectroscopy (NIRS) is used to quantify GLOBAL changes in oxy-hemoglobin (HbO) and deoxy-hemoglobin (Hb) concentrations in tissue. Errors that resulted from analyzing FOCAL changes in HbO and Hb concentrations were examined. It was found that the measured focal change in HbO and Hb was linearly proportional to the actual focal changes but that the proportionality constants were different. Thus relative changes in HbO and Hb cannot, in general, be quantified. This builds the case for diffuse optical tomography (DOT) which in general should be able to quantify focal changes in HbO and Hb through the use of image reconstruction algorithms that deconvolve the photon diffusion point-spread-function. The differences between NIRS and DOT using a rat model of somatosensory stimulation have been demonstrated.

In the above figure we overlay the source-detector geometry on the 830 nm absorption image of focal activation in the rat cortex to reveal the relative positioning of each optode. In graph *a* we plot the ratio Δ[HbO] / Δ[Hb] measured between source 2 and each detector separately. For comparison, the ratio of concentration changes determined by DOT is also graphed *b*. The main feature of the figure is the significant difference in the ratio for each source-detector pair. Interestingly, the ratio consistently decreases as the detector is moved further from the focal hemoglobin concentration increase.

These trends reveal the underlying problem associated with using NIRS, i.e. that the result is dependent on the positioning of the optodes relative to the focal change.

The DOT absorption coefficient images (at 830 nm) show a clearly detectable focal activation in the somatosensory cortex that is correlated with the 45 sec duration of forepaw stimulation. The calculated values of Δ[Hb] and Δ[HbT] relative to the baseline values agree well with the fMRI measurements previously made at the NMR Center. This result serves as the first cross-validation of the quantitative accuracy of DOT and fMRI.

A numerical method for calibrating the unknown coupling coefficients from a single measurement set, as opposed to the traditional experimental approach of separately measuring the coupling coefficients using a different measurement set (and usually different measurement protocol) has been developed. This new method is potentially

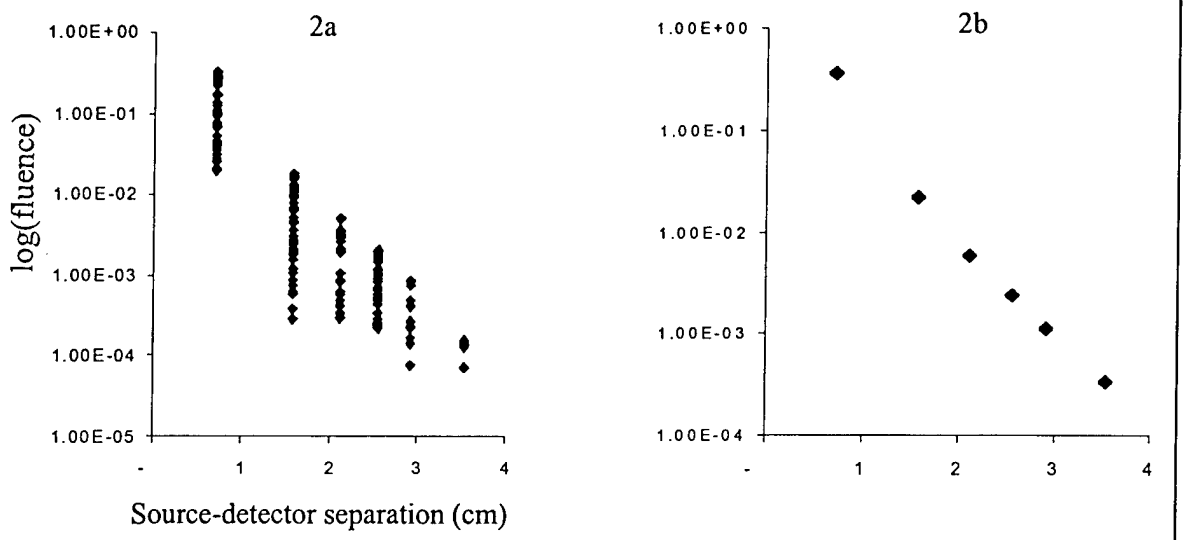


Figure 1. Fluence rate vs. source-detector separation with (2a), and without (2b) applying the calibration procedure

superior to the traditional method as it is possible for coupling coefficients to vary from measurement to measurement (e.g. due to perspiration or fiber movement) which would introduce systematic errors with the traditional calibration method. However, the new method does require that measurements for each source/detector be made with detectors/sources at two or more separations. In general, such measurements are the rule rather than the exception for diffuse optical tomography. In the phantom and simulation studies, the optical probe had nine sources in a 3x3 square grid centered in a 4x4 square grid of sixteen detectors. The grid spacing was 1 cm. Measurements were acquired for the 144 unique source-detector pairs. By fitting the 2D-reflectance measurement to the forward calculation, the optical scattering and absorption coefficient of the phantom as well as the coupling coefficients for each channel were obtained. The calibrated coupling coefficients were then used in reconstructing diffuse optical images of absorbing objects inside the phantom. Analysis revealed that this new calibration method has the potential to significantly improve the quality and accuracy of diffuse optical tomography.

Simulation was done to show how this calibration procedure will help to normalize the experimental data. The coupling coefficient for each source-detector pair changes randomly from 0.3 to 1.0 with 1% noise added to the calculated fluence rate. In the figure below, we plot the raw detection data vs. the source-detector separations. Without calibration, the data are scattered due to the randomly distributed coupling coefficient which give a very noisy background. After the calibration, the measurement is well normalized and the baseline becomes 'clean'. The details of how this method works have been submitted in a manuscript to Optics Letters.

Specific Aim 4: Determine clinical utility of diffuse optical tomography for stroke patients through human subject studies to identify sensitivity and specificity.

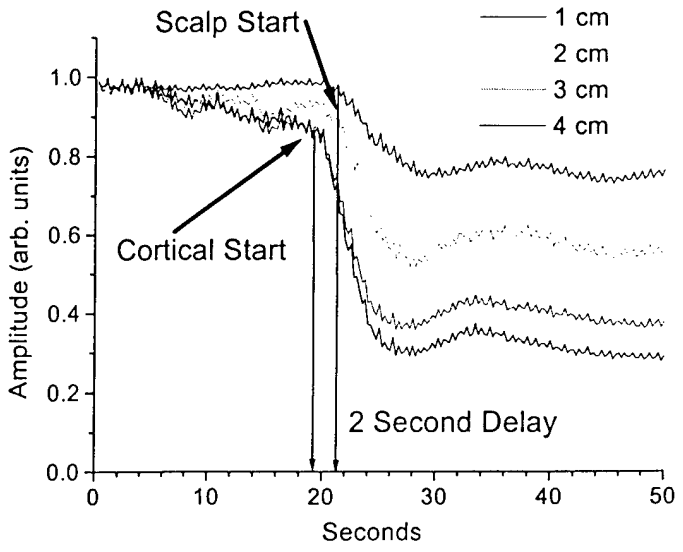


Figure 1 Attenuation of the diffuse optical signal due to passage of indocyanine green through the scalp and brain. Measurements were made with 4 different optode separations. The 2 second delay for small optode separations indicates the delayed arrival of ICG in the scalp relative to the brain.

Progress: A prototype near infrared imaging pad with multiple detectors and sources has been developed. Using this device the team was able to measure the inflow of intravenous injection of a clinically used dye, indocyanine green, and can now distinguish signals from scalp from brain blood flow. A 100 mW, 808 nm laser diode coupled into a 1 mm diameter fused silica fiber to deliver light to the scalp was used. Four photo-diode detectors were coupled to the scalp via 3 mm diameter plastic fibers. The collecting fibers were positioned 1, 2, 3, and 4 cm from the emitting fiber. These four separations were chosen to help discriminate between scalp signal and skull signal. Basically, measurements made with the 1 and 2 cm separation proved to be sensitive to the skull and scalp only, while measurements made at 3 and 4 cm are sensitive to the brain, skull, and scalp. The remitted diffuse intensity at these four positions was sampled at 4 Hz. Baseline data was collected for 10 seconds followed by the bolus injection. The bolus consisted of a 2 ml saline solution of 40 mg of indocyanine green injected into a vein in the arm of the volunteer. This injection was immediately followed by a 10 ml saline flush.

The observed decrease in the detected intensity due to the circulation of indocyanine green was detected 10 seconds following the injection of the bolus. The signal at 3 and 4 cm dropped significantly while the response at 1 and 2 cm was delayed by approximately 2 seconds. The delay at 1 and 2 cm indicates that the signal decay at 3 and 4 seconds for the initial 2 seconds is entirely due to the arrival of indocyanine green in the brain as opposed to scalp.

Plan: For the coming year, plans include completing a preliminary analysis of animal studies to investigate the sensitivity of diffuse optical tomography for detecting brain hemorrhage, and initiating experiments to investigate its sensitivity for detection and mapping of brain ischemia.

3.0 TRAUMA AND CRITICAL CARE FOCUS AREA

Task 1: Application of Microwave Imaging to Rapid Non-Invasive Detection of Intracranial Hematoma

The team has fully completed *in vitro* and are near completion of the *in vivo* evaluation of the microwave hematoma detection system (HDS) as it applies to intracranial hematomas. *In vitro* testing was begun using cadaveric pig brains. Results from this work demonstrate that the HDS can differentiate hematomas from brain and skull. Subsequently, *in vivo* study was performed in live anesthetized pigs. These studies showed that the HDS can accurately detect the presence of hematomas at epidural, intraventricular and intraparenchymal sites in a clinically relevant model. Subdural evaluation will be completed shortly.

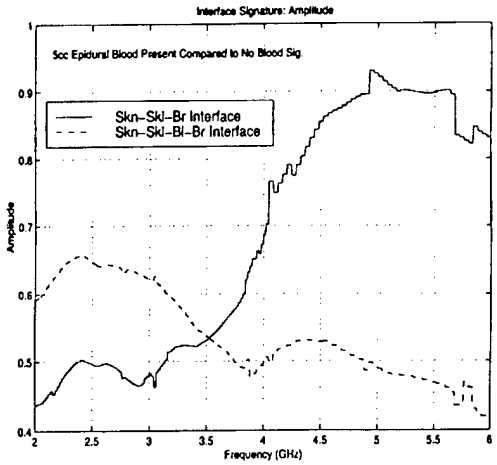
This CIMIT-sponsored work demonstrates that a new approach to noninvasive diagnosis of brain injury is feasible. The microwave HDS has significant potential for use as a tool for detecting intracranial hematomas. The next aspect of this study will be clinical trial and work to determine if other clinical conditions associated with trauma can be diagnosed using this device.

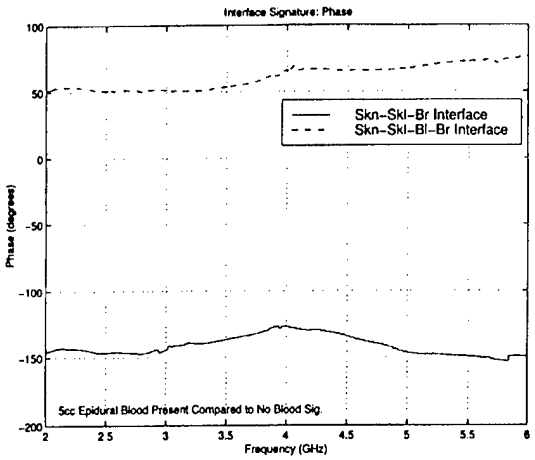
Specific Aim 1: To determine whether a hematoma detector based on microwave technology can detect the presence of blood in the epidural space.

Progress: Male Yorkshire pigs weighing from 25-50 kg were used in these studies. There were 5 pigs subjected to each test volume. Each pig was premedicated with ketamine and xyloxine I.M. followed by pentobarbital I.V. as an anesthetic. A catheter was placed surgically through a burr hole into the epidural space. Interrogation using the microwave HDS was performed prior to introduction of blood so that each animal could serve as its own control. Subsequently, either 2cc, 5cc or 10cc of autologous blood was administered via the catheter into the epidural space. Shortly after treatment, each pig was again interrogated using the microwave HDS. The HDS antenna was held 6 inches away from the pig's head.

Raw data was collected using a network analyzer. Data was processed using the MUSIC algorithm and the MATLAB computer program. The data was displayed as amplitude or phase as a function of radio frequency. Both real and imaginary data were used. Investigators analyzing the raw data were blinded to the treatment. Post-mortum analysis was performed to verify hematoma location.

Results: Following administration of epidural blood, there is a shift in both amplitude and phase from control (figures below). The shift is significant at 5cc and 10cc volumes. At 5cc, the shift is approximately 2-fold for amplitude and 2-fold for phase. Although there was a shift noted at 2cc, it was not found to be significantly different from the control.





Epidural hematoma , 5cc

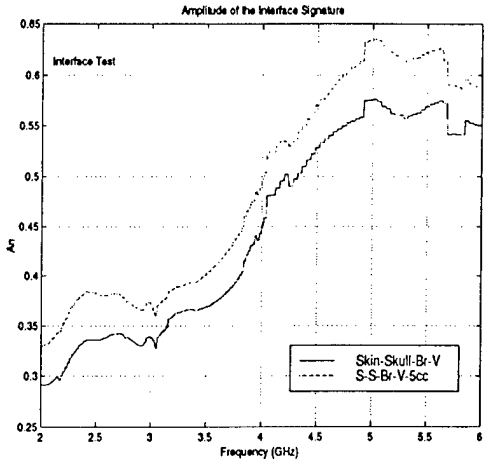
Epidural hematoma, 5cc

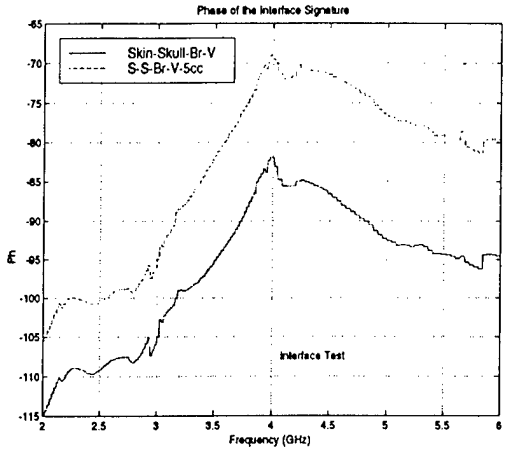
Problems: Due to a change in institutional policy, CT scans were unable to be performed. A post-mortem analysis to confirm the locations of the lesions was used.

Aim 2: To determine whether a hematoma detector based on microwave technology can detect the presence of blood in the lateral cerebral ventricles.

Progress: Methods were similar to those summarized above in Aim 1. The exception was that the catheter was placed surgically into the left lateral cerebral ventricle. Placement was confirmed by the return of CSF that had a pulsatile flow. Interrogation using the microwave HDS was performed prior to introduction of blood so that each animal could serve as its own control. Subsequently, either 2cc, 5cc or 10cc of autologous blood was administered via the catheter into the intraventricular space. Data collection and management was identical to that described for previous aims. Post-mortum study was also performed to confirm the placement of lesion.

Results: Following administration of intraventricular blood, there was a shift in both amplitude and phase from control. The shift was significant at 5cc and 10cc volumes. At 5cc, the shift was approximately 10% for amplitude and 10% for phase (Figs 3 and 4, respectively). Although there was a shift noted at 2cc, it was not found to be significantly different from control.





Intraventricular hematoma, 5cc

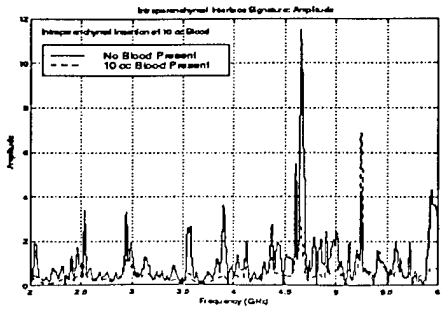
Intraventricular hematoma, 5cc

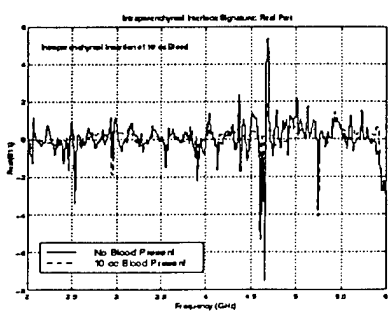
A post-mortem analysis to confirm the locations of the lesions was used.

Specific Aim 3: To determine whether a hematoma detector based on microwave technology can detect the presence of blood in an intraparenchymal location.

Progress: Methods were similar to those summarized above in Aim 1. The exception was that the catheter was placed surgically into the left frontal lobe. Interrogation using the microwave HDS was performed prior to introduction of blood so that each animal could serve as its own control. Subsequently, either 2cc, 5cc or 10cc of autologous blood was administered via the catheter into the intraparenchymal space.

Results: Following administration of intraparenchymal blood, there was a characteristic shift in both amplitude and phase from control. The shift occurs in a narrow frequency range, 4.6 to 4.7GHz. It is apparent at 5 and 10cc volumes. At 10 cc, the shift is approximately 3-fold for amplitude and 3-fold for real part (Figs 5 and 6, respectively). Although there was a shift noted at 2 and 5cc, it was not found to be significantly





Intraparenchymal hematoma, 10cc Intraparenchymal hematoma, 10cc

Post-mortem analysis was used to confirm the locations of the lesions.

Plan: Initial studies in animals demonstrate that the microwave HDS has significant potential for clinical utility. Determining if the microwave HDS can be used to diagnose intracranial hematomas in human patients will be accomplished in a clinical trial. Additionally, work is planned to determine if the microwave HDS can be used for clinical management of other clinical conditions associated with trauma

Task 2: Near-Infrared Reflectance Spectroscopy (NIRS) to Assess Regional Ischemia both during Trauma Resuscitation and at the Bedside in the Intensive Care Unit

The application of NIRS for the assessment of liver dysfunction during hemorrhagic shock has been described. Initial observations included the confirmation of previous experiments corroborating the use of our NIR probe for the non-invasive assessment of hepatic acidosis. Furthermore, by studying oxygen extraction from the liver, it was showen that hepatic acidosis is a more reliable end point of resuscitation in shock than tissue oxygenation. In a second set of animal experiments it was shown that the use of this probe allowed for simultaneous determination of hepatic venous oxygen saturation, hemoglobin and hepatic tissue pH with near infrared spectroscopy during hemorrhagic shock.

The overall objective of this research effort is to use NIRS and other NEW minimally invasive technology to determine the severity and reversibility of hemorrhagic shock by means of assessing organ specific cellular function and metabolism.

Although there are plans to continue the development of new probes for the assessment of gut and peripheral muscle as initially proposed, the original Umass designed probe for solid organ NIRS studies

Specific Aim 1 Use NIRS and other minimally invasive technology to determine the severity and reversibility of hemorrhagic shock by means of assessing cellular function and metabolism.

The goal of this research was to demonstrate that changes in liver pH during hemorrhagic shock are greater than pH_i changes suggesting that the liver may be an optimal organ to monitor splanchnic hypoperfusion and that an optical probe based on near infrared spectroscopy (NIRS) is applicable for continuous monitoring of liver pH .

Progress: In 6 pigs a tonometrics catheter was used to measure pH_i. A laparotomy was performed to place intraportal, and suprahepatic catheters to assess O_2 saturation and content. Intrahepatic tissue pH and NIRS measured liver pH were recorded continuously during hemorrhagic shock (45 minutes at a BP of 45-mm Hg). Resuscitation was achieved with shed blood and R Lactate.

Results: Changes in liver pH are more sensitive to blood loss than pH_i ($p = 0.03$). Good correlation was achieved between electrode pH and NIRS pH for each pig (R^2=0.89) and the estimated measurement accuracy was 0.03 pH units. The figures below indicate the relationship between liver pH and oxygen extraction ratio (OER) in the portal vein and suprahepatic veins, as well as pH_i and BP. OER plateaus soon after hemorrhage and fails to increase despite prolonged hypotension. However, liver pH continues to decline despite restoration of OER and systolic blood pressure. Liver pH is not fully recovered until 45 minutes after resuscitation.

Figure 1

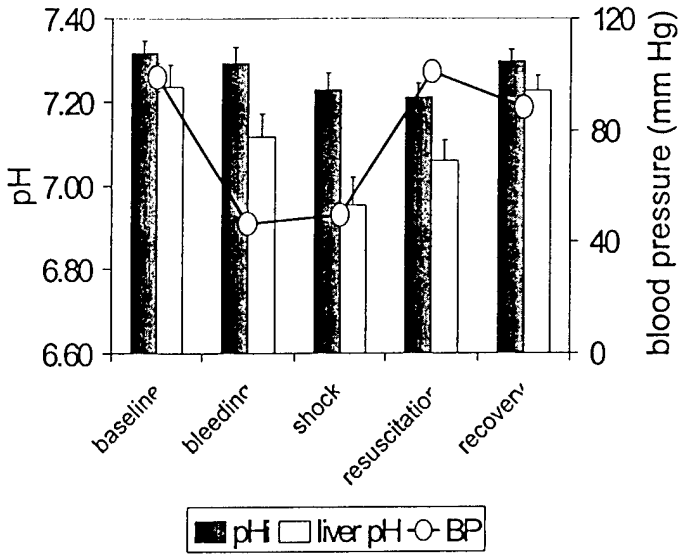
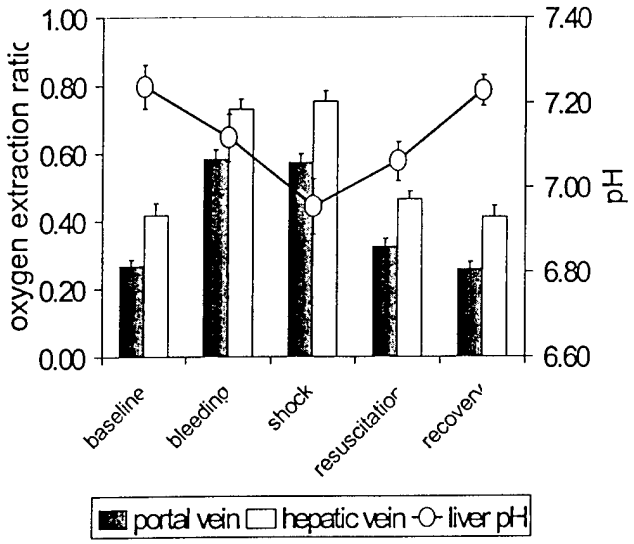


Figure 2



These data suggest that NIRS measured liver pH during shock closely follows electrode measured pH. In addition, muscle pH is a surrogate of gastric pHi in this model. Liver pH may be a more accurate indicator of the severity of shock than pH_i or OER and hence a better end point of resuscitation. Moreover, it could potentially be monitored with minimally invasive NIRS.

Specific Aim 2: To determine hepatic oxygen content as a measure of hepatic oxygen availability.

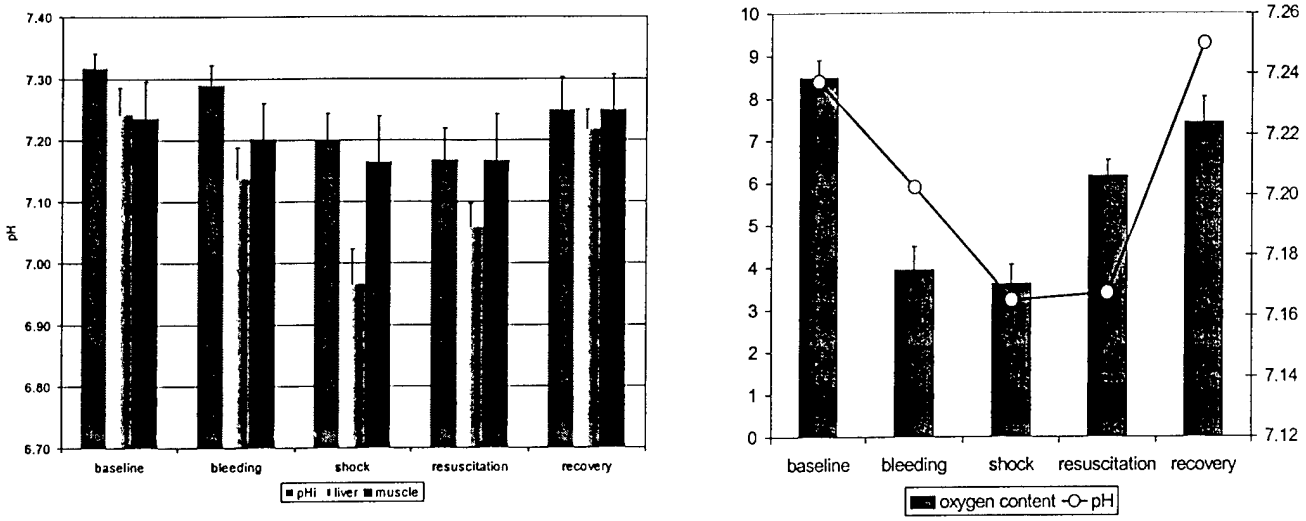
In addition to hepatic tissue pH, oxygen content may provide a measure of anaerobic metabolism, to indirectly quantify hepatic anaerobic metabolism in real time. Such information may provide a clinical tool to guide successful resuscitation.

Progress: Pigs (n=6) underwent hemorraghic shock by lowering their MAP to 40 mm Hg for 45 min. During shock and recovery tissue pH was measured using microelectrodes and hepatic venous blood was collected every 5 minutes. Oxygen saturation and hemoglobin were determined with a co-oximeter and used to calculate oxygen content. NIR spectra were collected every 30 sec using a fiber optic probe placed on the surface of

the liver. Calibration equations were derived for each pig using partial least squares to relate the NIR spectra to the reference pH and blood measurements. The accuracy of the calibration equations was assessed using cross validation techniques. Continuous oxygen content, calculated from spectra, was compared to pH.

Results: The average correlation coefficients between NIR and reference measurements were 0.78, 0.68 and 0.93 respectively for pH, Hb and S_vO2. The estimated accuracy of the technique, given by SECV (standard error of cross validation), was 0.03 pH units, 0.32 g/dL and 6%. Comparison of continuous measures of pH and oxygen content showed that in some pigs pH did not return to baseline until late in the recovery period, despite a rapid return in oxygen availability.

Figure 3



The data suggest that NIRS can be used to determine and compare hepatic tissue pH and oxygen content. Delayed or incomplete recovery of pH may be an indication of the cells' inability to utilize available oxygen. NIRS has potential application as a clinical tool to gauge the effectiveness of resuscitation.

Plan: To continue the development of new techniques for the assessment of "in vivo monitoring" of specific organs during ischemia and shock in trauma and critically ill patients. To continue to incorporate other parameters of tissue perfusion and oxygenation as well as biochemical markers of ischemia and reperfusion in this and several other models including mitochondrial function of gut and liver. Endoscopic assessment of the small bowel and colon as well as trans-cutaneous measurements of peripheral muscle in critically ill patients will be included in a renewal application.

Task 3: Noise-Enhanced Tactile Sensation for the Management of Sensory Deficits in Patients with Stroke

This project has been progressing on on hold since June, 1999 pending notification from the HSRRB of the Department of Defense.

Specific Aim 1: Design and construct a suitable apparatus for patient experiments.

Progress: A personal computer, with a digital to analog (D/A) converter (CIO-DAS 1600 board, ComputerBoards, Inc., Mansfield, MA) was installed in the Motor Control and Sensory Enhancement Laboratory at Spaulding Rehabilitation Hospital along with a force-controlled, DC motor (Series 300B Lever System, Cambridge Technology, Watertown, MA) stimulus isolator and oscilloscope. The motor was tuned and calibrated and software, which had been used in previous experiments involving young healthy subjects, was modified to provide longer reaction times and better visual feedback for subjects with stroke.

Specific Aim 2: Demonstrate the feasibility of both the apparatus and an experimental protocol through implementation in patients with stroke; collect data on patients with stroke.

Progress: At the point at which the study was placed on hold, twenty-one subjects had been screened for the project which included a mental status examination and a comprehensive battery of sensory tests of both hands. Sensory tests included light touch with mono-filaments, hot-cold and 2 point discrimination, proprioception and muscle strength testing. Seven subjects qualified to participate in the experiment. These seven subjects were tested on both the affected and unaffected sides at two different noise levels (50% and 100%). The unaffected side was always tested first to ensure that the subjects had a complete understanding of the testing protocol in the hand with normal sensation.

Specific Aim 3: Analyze data to test the hypothesis that electrical noise can enhance the ability of patients with stroke to detect subthreshold mechanical stimuli.

Progress: It was demonstrated in the seven subjects that electrical noise can in fact slightly enhance the ability of patients with stroke to detect subthreshold mechanical stimuli. Specifically, it was found that there was a 13.9% reduction in subcutaneous sensation threshold with electrical noise. Three subjects remain to complete the analysis. The original protocol has been modified to test the effect of mechanical noise, which, based on our preliminary results and those of other studies, is believed to have an even stronger effect.

Plan: To resume and complete study.

2.5 NEW INITIATIVES CLINICAL FOCUS AREA

Task 1: Automated Acquisition, Assay and Interpretation of Blood Samples

Specific Aim 1: Provide a proof-of-concept demonstration of the ability to obtain real-time assay, via the use of IgG, TNF, or IL.

Specific Aim 2: Optimize the design of a post-processing system that accurately and robustly identifies the contents of the blood.

Specific Aim 3: Assess the feasibility of developing a decision-assist system capable of rendering treatment advice from the assay results and other observations.

Progress: The progress and plan for this project are reported with the Microsensors ATT in Section 4.3.

Task 2: Endoscopic Retrograde Cholangio-Pancreatography (ERCP) Simulator

The ERCP Simulation project aims to develop a computer-based training tool for upper-GI endoscopy that features lifelike animation, realistic haptic interfaces, and an integrated fluoroscopic simulator for the biliary and pancreatic anatomy.

Specific Aim 1: Begin the development of an upper-GI endoscopy graphical simulator.

Specific Aim 2: Modify a previously developed cardiology synthetic fluoroscopy simulator for the biliary and pancreatic anatomy.

Specific Aim 3: Develop haptic interfaces for both GI endoscopy and fluoroscopy, as well as extend existing interfaces to incorporate two-point grasping of simulated organs (in concert with Simulation ATT).

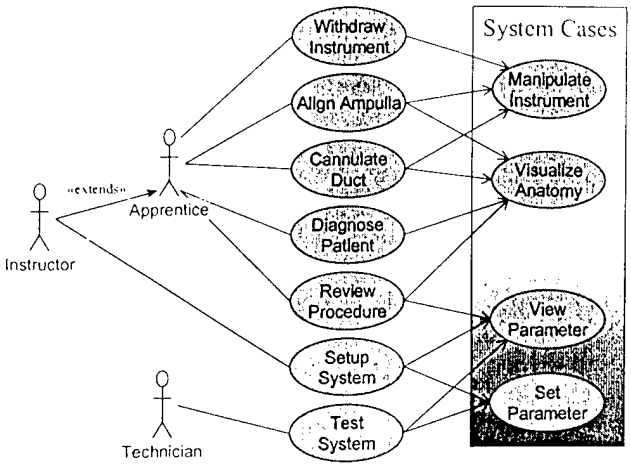
Specific Aim 4: Develop a means for characterizing linear and non-linear deformation of tissue models (in concert with Simulation ATT).

Specific Aim 5: Begin integration of GI graphical simulator, fluoroscopic simulator, and haptic simulator.

Specific Aim 6: Initiate educational content gathering for incorporation into the final product.

Progress: Preliminary efforts were focused on understanding the critical aspects of the ERCP procedure. To accomplish this objective, time was spent with domain experts. This included detailed discussions of end-user expectations for the product and observation of actual ERCP procedures performed under the direction of Dr. Robert Schapiro in the Endoscopy Unit of MGH.

User processes that emerged from the analysis (e.g. positioning of the endoscope in alignment with the ampulla) led to identification of the critical system cases that must be supported. The figure to the right shows the relationship between the operators, user processes, and their enabling system cases.



Operators, user processes, and the system cases that enable them.

Processes have been identified that support the following capabilities:

1. apprentice training by an instructor, who can customize aspects of the procedure and review performance.
2. system testing and maintenance by technical staff.

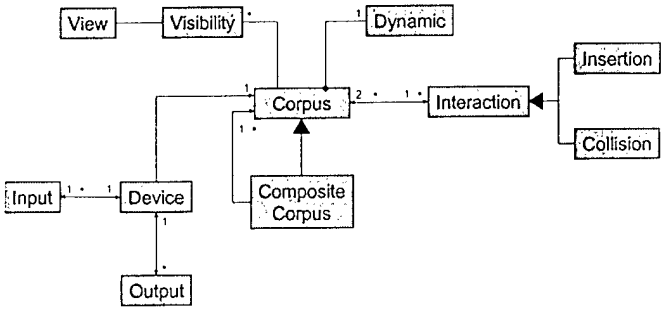
Domain Analysis: Ongoing analysis of the domain has led to a system concept that centers on the generalized body, or *corpus*, as shown in the figure below. Each corpus contains a dynamic model, a visibility, and a list of interactions with other corpora.

Complex objects result from the connection of many simple corpora. The endoscope, for example, is modeled using a discrete number of rigid links, connected by flexible joints of known stiffness. Other extended bodies include the catheter, esophagus, stomach, and duodenum. In general, interaction refers to any application of force from one corpus to another. One example of an interaction is the permanent connection between the elements of a linked rod model of an endoscope. Interactions between corpora may be specialized according to situation, however. Temporary interactions include the collision between the tip of an endoscope and stomach wall and the insertion of a catheter into the biliary duct.

Endoscopes, fluoroscopes, and sphincterotomes differ from anatomical constructs by having inputs and outputs, the latter only if a haptic interface applies.

Haptic Interface Design

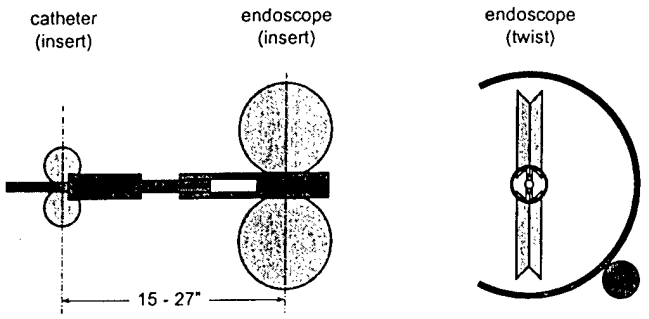
Early thoughts on the ERCP simulator specified the purchase of a PHANToM haptic interface, commercially available from SensAble Technologies, Inc. Though applicable to problems with rigid tools such as laparoscopic surgery, the PHANToM is ill suited to the task



Conceptual diagram of classes that result from domain analysis.

of providing force feedback through a flexible body such as endoscope or catheter.

To address this issue, Draper Laboratory staff mechanical engineer Stephen Bellio is designing a haptic interface suitable for flexible tools, shown conceptually in figure. The interface contains two axial reactors to counter insertion forces of both endoscope and catheter and a single torsion reactor to counter the twisting moments of the endoscope.



Preliminary design for haptic interface. Axial reactors serve the insertion of catheter and endoscope and a torsion reactor serves the twist of the latter.

Anatomic Modeling: Segmented voxel data from the Visible Human project has been purchased from Gold Standard Multimedia, Inc. Draper imaging specialist Anthony Sacramone has begun constructing a polygonal model suitable for dynamic interaction and endoluminal viewing from these data. In particular, the open-source Visualization Toolkit (VTK) package has been installed on project computers and its contained marching cube algorithm is under investigation as a means of converting voxels to polygons.

Task 3: Gene Delivery/Activation

Specific Aim 1: To develop novel polymer-based gene delivery system in conjunction with the Biomaterials ATT.

Progress: This proposal (Polymer-based Gene Delivery Platform) is being developed under the Biomaterials ATT and will be approved for year two funding (see 4.1 Biomaterials ATT).

Task 4: Endoscopically Assisted Mandibular Distraction Osteogenesis

Specific Aim 1: To develop a totally buried, miniature, remotely activated distraction device with accurate three dimensional vector controls.

Specific Aim 2: To develop minimally invasive surgical techniques for distractor placement.

Specific Aim 3: To develop methods to control and enhance the wound healing process in order to shorten the overall treatment duration.

Progress: The feasibility of endoscopic placement of a semi-buried device has been developed.

Plan: To further develop a totally buried device, and to continue research on speeding the healing process and optimization of surgical instrumentation and approach in micro

pigs. Additionally, there will be a focus on the development of an application for the planning and simulation of an osteotomy and analysis of the results.

Task 5: Lung Volume Reduction Using a Bronchoscopic Approach

The objective of lung volume reduction is to eliminate dysfunctional, overinflated regions of lung. Results similar to surgery with resection have been obtained by plication and stapling without tissue removal, as well as laser directed tissue obliteration. These observations suggest that removal of the dysfunctional tissue is not required. A procedure that eliminates the participation of dysfunctional tissue in the breathing process would suffice.

Specific Aim 1: Compare short term (1 month) and long term (3 month) survival, physiological responses, surgical complications and lung histopathology in control sheep (untreated, non-emphysema) following either standard surgical plication lung volume reduction or bronchoscopic lung volume reduction (BVR).

Specific Aim 2: Compare short and long term survival, physiological responses, complications, and lung histopathology in sheep with emphysema (generated by Papain exposure) treated either with SPVR or BVR.

Progress: CIMIT researchers have developed a method whereby such regions can be eliminated bronchoscopically without tissue resection. Target regions will be permanently collapsed and scarred over using a biopolymer that can be injected through the bronchoscope, and act like glue. This fibrin-based polymer, which has been tested in isolated cow lung preparations, will be studied in a sheep model of emphysema to further evaluate its safety and effectiveness relative to conventional LVRS. It is anticipated that these initial studies will serve as a basis for longer term large animal studies, and eventually result in testing in humans.

Plan: If the sheep experiments are successful, the work focus will be directed optimizing the procedure in animals, and transferring the procedure to clinical use.

3.0 TECHNOLOGY ASSESSMENT AND OUTCOMES ANALYSIS PROGRAM

The Technology Assessment and Outcomes Analysis Program was established in order to facilitate accurate and expeditious evaluation of new technologies as they are developed and implemented. The intent was to develop a program that is fully integrated with all CIMIT research, education, and clinical activities. The Program's principal activities include decision analysis, cost-benefit and cost-effectiveness analysis, and outcome analysis. These are carried out in order to help CIMIT with the following:

Specific Aim 1: Focus the allocation of resources for the development of new diagnostic and therapeutic technologies.

Specific Aim 2: Facilitate rapid and accurate assessment of procedural efficacy and patient outcomes.

Specific Aim 3: Demonstrate the value of these technologies to the public, physicians, payers, and legislators.

Progress: The Program now includes 7 individuals with training and expertise in the core disciplines of biostatistics, epidemiology, economics, decision science, outcomes analysis, and health care policy, and provides the infrastructure and expertise to properly evaluate minimally invasive diagnostic and therapeutic procedures at all stages of development. A unique focus of the CIMIT program is the concentration on the evaluation of technologies during their early stages from discovery to preliminary clinical testing, when extensive data regarding clinical effectiveness may not yet be available.

An economic model of patient behavior when faced with the choice of undergoing a risky intervention has been developed and data are being collected in order to test the predictions value of the model. Substantial progress has been made on the formation of a database which covers over 5000 patients receiving treatment for any cerebrovascular disease at MGH during the fiscal years 1995 to 1998. This database will provide the basis for answering many questions about stroke treatment at MGH and enable the program to provide real time analysis as new stroke interventions & diagnostic tools move from the bench to their clinical applications.

A cost-effectiveness analysis of percutaneous abdominal stent placement in patients with abdominal aortic aneurysm has also been initiated. This project involves a comparison of the cost-effectiveness of this minimally invasive therapy to open surgery, and includes an analysis of the impact which the availability of this new technology might have on patient survival and costs, as well as the population-wide effects which changing indications for treatment could have. Preliminary data collection and modeling have been completed; additional, prospective data collection is ongoing.

In the area of cancer diagnosis and treatment, the cost-effectiveness of surgical management strategies for patients with liver metastases from colorectal carcinoma has been investigated, and expansion of the analysis to include minimally invasive therapies such as percutaneous in-situ tumor ablation using radiofrequency energy has been started. Investigation of the relative benefits and costs of strategies for imaging and surgery in patients with pancreatic cancer has also begun.

Finally, the program has recently begun to study the dynamics of medical technology diffusion, using the tools of complexity science and agent-based simulation. The goal of

this project is to model the environment in which new medical technologies are brought into routine clinical practice, in order to better understand the factors which lead to more rapid uptake of beneficial technologies. In so doing, it is hoped that CIMIT might be better able to position CIMIT-developed technologies for success in the medical marketplace.

Plan: To date, activities have focused primarily on two specific CIMIT Clinical Focus Areas (CFA's): Stroke and Cancer. By working with investigators in each of these CFA's the program has developed economic and outcome models, in order to perform detailed analysis of the costs and outcomes associated with the use of technologies under development. It is anticipated that during the coming months efforts in these area will expand, and that opportunities to work with investigators from other CFA's and ATT's will begin.

4.0 ADVANCED TECHNOLOGY TEAMS

Advanced Technology Teams (ATTs) act as a resource for technologically challenging problems within CIMIT, support the technical activities of CFAs, and develop key enabling technologies to increase quality or decrease cost of clinical care. During Year-1, a core group of investigators was established to pursue key enabling technologies that have the potential of making a major impact on the way healthcare is delivered in the future. The organizational structure of the Advanced Technology Teams has continued to be refined to achieve greater synergy. (See below for most current, Q4 organization.) Conceptually, we have developed two types of ATTs have been developed: ones that require technological advancement in order to become feasible, and ones that represent a CIMIT core capability but do not require advanced research at the present time. The research activities that comprise these ATTs are described in the following subsections. More specifically, research projects have been initiated in:

- Biomaterials (Langer, MIT)
- Image guided therapy (a new aggregation of the Artificial Intelligence and Surgical Planning ATTs in the original proposal) (Kikinis, BWH)
- MicroSensors (Cunningham, DL)
- Simulations (Dawson, MGH)
- Tissue engineering (Vacanti, MGH)

Collectively, new advancements in these technological areas will lead to major new therapies and treatment modalities. These ATTs are complemented by more diffuse activities in the following core areas:

- Endoscopic tools (Isaacson, MGH)
- Energy delivery (Nishioka, MGH)
- Medical imaging (Rosen, MGH)
- Minimally invasive interventional devices (Oesterle, MGH)

These teams, while in place and providing support to other projects (for example, endoscopic tools supports the Cardiovascular CFA project "Detection of Vulnerable Plaque Using Optical Coherence Tomography (OCT)"; energy delivery supports the Cancer CFA project "Early Detection and Ablation of Epithelial Cancers"), do not at this time themselves represent focused ATT research activities.

4.1 Biomaterials

Task 1: Degradable Conductive Polymers

Specific Aim 1: Electroactive polymers which constitute an unique class of synthetic polymers posses the ability to inter-convert chemical, mechanical, thermal, and optical perturbations into tiny electrical currents. This property can be exploited to play an important role in the interfacing of the external environment with biological systems.

Electronically conductive polymers are especially attractive in that they can not only be employed as guidance channels or substrates for tissue culture, but can also potentially be utilized as a medium to subject the adhered tissue to an electrical stimulus. The primary goal of this research is to synthesize degradable analogs of the conductive ploymer PPy, as well as water soluble analogs. Furthermore, this project will study the degradation and cytocompatibility characteristics of these polymers.

Progress: This project was recently approved by the SMC and is scheduled to begin in Year-2.

Task 2: Polymer-based Gene Delivery Platform

Specific Aim 1: The long-term goal of this project is to create a potentially safe synthetic gene delivery system with high transfection efficiency for the local vascular delivery of plasmid DNA. To accomplish this goal, we will synthesize a polymer-based gene delivery system that on the molecular level mimics viruses, i.e., capable of condensing and encapsulating DNA, entering cells via endocytosis, and escaping the endosomal compartment to release the DNA into the cytoplasm.

Progress: This project was recently approved by the SMC and is scheduled to begin active work in the next quarter. This project is being presented to the CIMIT Forum on October 5, 1999.

4.2 Image Guided Therapy

Task 1: Segmentation of Bone From CT and Vessels From MRA Data

Specific Aim 1: *Implementation of Image Enhancement Scheme.* Specific Aim 1 is to implement an image data enhancement scheme for segmentation of bone from CT and vessels from MRA. The proposed method will be based on adaptive filtering, a methodology that modifies the filtering strategy locally in space in order to tailor it to the specific nature of the signal in that region. This flexibility sets this filter approach apart from conventional shift invariant filtering. In order to make this software useful in a clinical environment, we also plan to develop a graphical user interface. The proposed methods will serve as an important module in an existing segmentation pipeline which we expect will significantly improve the precision of bone and vessel segmentation, especially for surgical visualization.

Progress: The first milestone, implementation of adaptive filtering scheme, has been finalized. The Matlab version of the adaptive filtering algorithm has been implemented in C-code . A library of patient data sets that will be used in the validation part of the project is being assembled.

Plan: In broad terms, there are two types of computers in our laboratory. The first type is desktop workstations with high-end graphic capabilities. The second type of machines in our laboratory are equipped with high-end multi-processor capability. The plan is to parallelize the developed C-code using Solaris Posix Threads to take advantage of the multi-CPU architecture of the servers. This will significantly speed up the algorithm.

Specific Aim 2: Involves determining how to quantitatively validate automated segmentation method results. The plan is to quantitatively validate automated segmentation method results by comparing them with manual segmentation performed by trained expert. It is expected that our automated method will provide results comparable to results obtained by tedious, labor intensive, and expensive manual post-processing of thresholded MR angiograms. Furthermore, it is predicted that the automatic method will outperform manual segmentation in terms of reproducibility and efficiency. The validity of the segmentation results from our automated method will be defined as the percentage of voxel-to-voxel overlap with the same data manually segmented. The algorithm will be tuned to maximize this value over a large set of data.

Progress: There is a set of operating parameters which control the overall behavior of the adaptive filtering scheme. The task of explicitly identifying the more important parameters in order to find an optimized parameter combination for vessel and bone segmentation respectively has begun. It has been found that the parameters that most effect the overall performance of the adaptive filtering scheme are: (1) the transition frequency between the low-pass and the high-pass filters in the adaptive filter, and (2) the noise level parameter that defines what is noise and image structure in the data. The subproject, Development of a Framework for Optimizing Filter Parameters, will continue throughout the project as planned.

Plan: To validate the accuracy of the developed segmentation algorithms on patient data. In order to find an optimized setting for the most important parameters on the assembled a library of test data sets. Selection of the data has been done in close collaboration with our clinical partners. The intent is to select a few slices in each of the data sets in our test data library and then, manually outline critical areas on these slices. This will provide a gold standard which will be used as a criterion for finding optimized parameter settings. The semi-automatic procedures used in the surgical planning laboratory today (thresholding, connectivity, cleaning and mending in volume editor) will serve as a reference.

Task 2: Real-time Registration of Intra-operative Ultrasound with Pre-operative CT/MR for Image Guided Therapy

The utility of minimally invasive therapy depends, in no small measure, on the ability to precisely deliver therapy to the targeted site. The efficacy of image guided therapies is now well documented in the literature for such applications as tissue biopsy, cryotherapy, brachytherapy, and energy delivery. For the most part, however, image guidance requires expensive intra-operative equipment (e.g., intra-operative MRI), ionizing radiation (e.g., fluoroscopy, CT), or is limited to surface (e.g., luminal) imaging of areas accessible through videoendoscopic tools. Although inexpensive, non-ionizing, subsurface-capable, and portable, ultrasound imaging has not found the widespread usage that one might expect, due largely to the poor- contrast, specular noise, and unintuitive nature of ultrasound imagery. In this proposal we aim to demonstrate a novel new method for improving the visualization quality of intra-operative ultrasound imagery. Specifically, because of the overwhelming preference of users for high-contrast CT/MR imagery, and since such imagery are frequently acquired pre-operatively, we aim to demonstrate the ability to register these high contrast pre-operative imagery to yield the same view as the

intra-operative ultrasound. This approach enables, effectively, an intra-operative CT/MR imagery from which image guidance can be performed, but without incurring the costs and risks associated with continuous CT/MR imaging.

Specific Aim 1: Demonstrate the ability to register pre-operative CT/MR, in a non-real-time manner, so that point-to-point correspondence to an intra-operative ultrasound can be obtained.

Progress: The team has successfully utilized anisotropic diffusion to smooth the speckle noise component of ultrasound images while maintaining feature edge sharpness. The CT imagery was manually masked to highlight image features visible in ultrasound imagery; then anisotropic diffusion was also applied to determine edge strength. The edge strength functions of the ultrasound and CT images were then successfully registered automatically. Once this alignment was accomplished, the two imaging modalities were fused into a low-noise, high-contrast image. This research was presented at the SPIE Aerosense '99 Battlefield Biomedical Technologies conference in Orlando, FL, on April 5-9, 1999. Additionally, work on using mutual information in order to perform image registration has begun. At present, the team is still examining whether the mutual information approach can be made robust to differences in intensity variations between CT and ultrasound imagery.

Plan: To acquire higher quality digital ultrasound imagery to work in conjunction with 3-D CT data in the immediate future. Additionally, functionals capable of concurrently registering images as well as enhancing images will be explored.

4.3 Microsensors

Task 1: MEMS Technologies: Real-Time Blood Assay

The ultimate goal of this project is the development of a sensor technology capable of performing rapid analysis of the protein content of a patient's fluid sample.

Specific Aim 1: The primary aim is to measure cytokines in the circulating blood serum of a trauma victim that predict Multiple Organ Failure (MOF).

Progress: The sensor being developed is a micro-electro-mechanical (MEM) silicon membrane resonator called the "micro Chemical Analysis Array" (CANARY) that acts as a miniature, all-electronic platform for performing direct biochemical assays. Receptor protein coatings that selectively adsorb a particular target analyte from the blood sample are applied to the CANARY, which registers a shift in resonant frequency when the mass of the target analyte in incorporated into the receptor coating. Using this method, mass detection of ~10 picograms has been measured, corresponding to a resolution of 0.25 nanograms/ml of a typical antibody in aqueous solution.

With direction from Dr. J.C. Puyana and the Trauma CFA, cytokines that predict MOF were identified, and protein receptor materials for each were obtained. For proof-of-concept demonstration of the cytokine receptor immobilization chemistry, phosphate buffer solution (PBS) mixed with calibrated concentrations of target cytokines are used to test the sensor rather than blood serum. Through discussions with the BWH team, it

became evident that the ability to simultaneously monitor a host of cytokines would have tremendously higher predictive value than measurement of a single analyte. This realization made it necessary to consider miniaturization of the sensor to enable integration of several assays into the same silicon chip. Major progress has been made in the miniaturization of the sensor, which has enabled us to build sensor chips capable of measuring many protein analytes simultaneously. Individual miniature sensors and 8-element sensor arrays have been designed and built, along with the electronic circuitry and software necessary to read the sensor output, amplify it, and report it to a personal computer interface. The operation of the miniaturized sensor has been extensively characterized, and has been verified to posses mass detection sensitivity equal to the large sensor reported earlier.

In parallel to the sensor hardware development, progress has been made developing protocols for attachment of chemical protein receptors to the device. While many other research groups and companies have demonstrated surface activation with immobilized protein, the team faced the need to develop a procedure that would be compatible with the MEMS device and packaging. At this time, a receptor coating protocol has been developed and verified by ellipsometry measurements. The receptor coating procedure is now being applied to live miniature devices using a flow cell to expose the sensor. Response characterization to analyte test solution exposure is underway.

Specific Aim 2: Determination of Analytes of Interest and Detection Requirements

Progress: The trauma team at BWH identified several interleukins (IL-1, 2, 4, 6, 8, 10) whose elevated concentrations have been found to correlate positively with MOF. TNF-, which was originally thought to be the protein of main interest, was found not to have high predictive value. While blood was originally considered to be the primary analytical fluid, it is currently believed that urine would have equal value.

Several other analytes were also identified as materials of interest to the trauma team. Real-time determination of the concentrations of amino acids, antioxidants, enzymes and metabolites were also considered relevant to trauma diagnosis. At this time, however, the team chose to focus on interleukin detection because protein receptor molecules were readily available, and it was determined that larger molecules would be easier to detect with the sensor.

Simultaneous monitoring of several interleukins was considered to have much higher MOF predictive value than measurement of a single protein (TNF- was the sole analyte proposed originally). It was agreed that a sensor array would provide the greatest benefit. This decision would entail a significant change in direction, as a single sensor system was originally proposed. The development of a miniature sensor that could be configured into an array of 8-10 elements was pursued.

Specific Aim 3: Sensor System Development: A miniature version of the MEMS resonator sensor was designed, a new chip fabrication process was developed, and wafers were fabricated at Draper Laboratory's MEMS fabrication facility. 2-element sensor chips were built for sensor and electronics evaluation, and 8-element sensor chips were built to implement the array. A cross section diagram of the sensor is shown in the figure below, and SEM photos of a sensor within an array. The resonant modes of the sensor (without receptor coatings) were characterized, and found to conform closely with

predicted values, shown below. As shown, three resonant modes are excited within the sensor membrane. The task of the electronics and software is to identify and track the highest magnitude peak.

An electronic circuit to read the sensor output and amplify it was designed, built, and tested. Due to the small size of the sensor, additional amplifier gain was required compared to the original large sensor, and a great deal of effort was applied to reduce all noise sources within the circuit. The current readout circuit for a single sensor is implemented on a 4x4 inch breadboard that connects to a Hewlett Packard spectrum analyzer. We have recently completed fabrication of an electronic circuit that will enable sequential addressing of an 8-element sensor array.

In order to perform continuous monitoring of sensor resonant frequencies, and to perform tasks such as data compensation (i.e. for temperature) and data storage, a computer interface to the electronic circuit was implemented using LABView as a platform. The interface allows the user to operate the sensor hardware using cursor "point and click" buttons, and currently implements the most important functions of the spectrum analyzer. The computer interface allows monitoring and control of the chip temperature through two temperature sensors embedded within the sensor package.

Packaging methods were also developed for the miniature sensor. One significant difficulty was the implementation of epoxies (used to hold the sensor chip within the package) that do not leach material into the solvents used for fluid exposure. After experimentation, a suitable epoxy material was found, and methods for curing it without inducing significant stress in the sensor chip were developed. Likewise, implementation of flow cell hardware using materials that do not contribute chemical contamination to the sensor chip was an issue to contend with. Currently, high purity stainless steel fixures are used, with teflon tubing and viton gaskets. A "flow cell" was constructed that enables flow of a variety of liquids past the sensor surface while it is resonating.

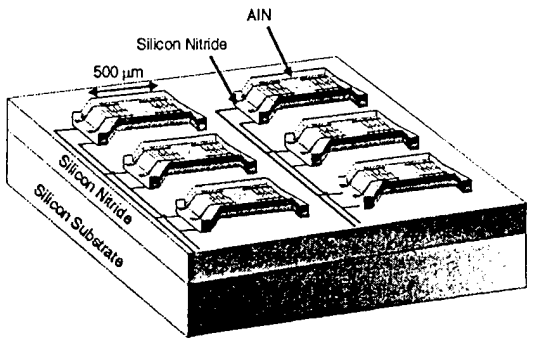


Figure
Schematic drawing of MEMS chemical sensor structure. The sensor is an thin film membrane resonator made of single crystal silison, a thin film piezeoelectric material, and two sets of interdigitated metal electrodes. An "alternate" process has been developed (not shown) that enables the receptor coating and analyte exposure to be performed through holes etched from the back surface of the chip.

Specific Aim 4: Sensor Surface Chemistry: The goal is to devise a "generic" method for preparing the sensor with a surface-immobilized interleukin antibody. Ideally, the surface activation protocol will be identical for every sensor, except for the application of the antibody material as a final step. One strategy that has

been used very successfully for assays has been to attach a biotin molecule to an inactive site of the antibody molecule. A surface activated with avidin has a very high affinity for the biotin, and binds the antibody in place, in the correct orientation for optimal interaction with the analyte. This method is so common, that thousands of antibodies – including antibodies for the interleukins of interest to us - can be commercially obtained in a "biotinylated" state. Therefore, the main goal of surface activation entails obtaining covalent attachment of an avidin monolayer to our MEMS resonator.

Progress: Early development of receptor surface chemistry involved attachment of receptor molecules to a bare silicon surface. This required silanation of the silicon surface – a chemical treatment process that involved baking the packaged sensor at an elevated temperature to obtain proper activation. The elevated temperature process was found to relax strain in the packaging materials, contaminate sensors with residues from the oven, and to result in unpredictable shifts in sensor resonant frequency.

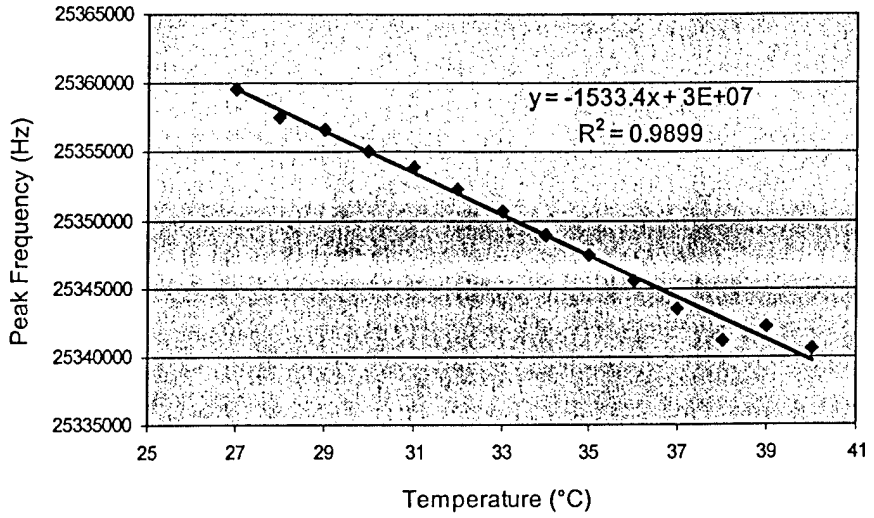
The MEMS sensor fabrication process was modified to include a thin gold layer on the active surface to facilitate the receptor binding process. The gold surface is activated at room temperature by an aminoalkanethiol compound, which sequentially binds to glutaraldehyde, avidin, biotinylated antibody, and finally the specific antigen. To test the effectiveness of the procedure, preliminary studies were conducted on dummy wafers with gold sputtered on the surface. These wafers were first tested with the coatings of biotinylated anti-dog IgG and dog IgG. Ellipsometry measurements were used to confirm that the bio-layers had been coated on the gold surface. The results indicated that the total thickness for the first several coating layers with biotinylated anti-dog IgG was 144 ± 84 Å (the standard deviation reflected the uneven coating on the 1/2" x 1/2" surface). When dog IgG was bound to the surface, the total thickness increased to 272 ± 145 Å. Control measurements were done by directly immersing the wafers in (1) biotinylated anti-dog IgG, and (2) first in biotinylated anti-dog IgG and then in dog IgG. The total thickness measured for these two cases were 45 ± 26 Å and 46 ± 23 Å, respectively.

The coating and exposure procedures were subsequently performed on live sensors using biotinylated Anti-Dog IgG as the receptor coating, and Dog IgG as the analyte. As shown, the resonant frequency of the miniature resonator is decreased by the subsequent additions of the avidin, biotinylated receptor protein, and the IgG analyte. This initial result indicates that a similar receptor application approach and exposure protocol will yield similar results for the detection of interkeukins.

Specific Aim 5: Sensor Characterization

Progress: The protein receptor immobilization and liquid analyte exposure testing presented under Specific Aim 4 were preceded by a battery of tests aimed at understanding the sensor's performance and sensitivity limitations. Initial testing of the device was performed without coatings. Temperature dependence of resonant frequency was measured (figure below) and temperature control hardware was implemented with the ability to keep chip operating temperature within 0.1 C of a target value. The data in the figure below were taken when the sensor was exposed to air using open-loop setup. It

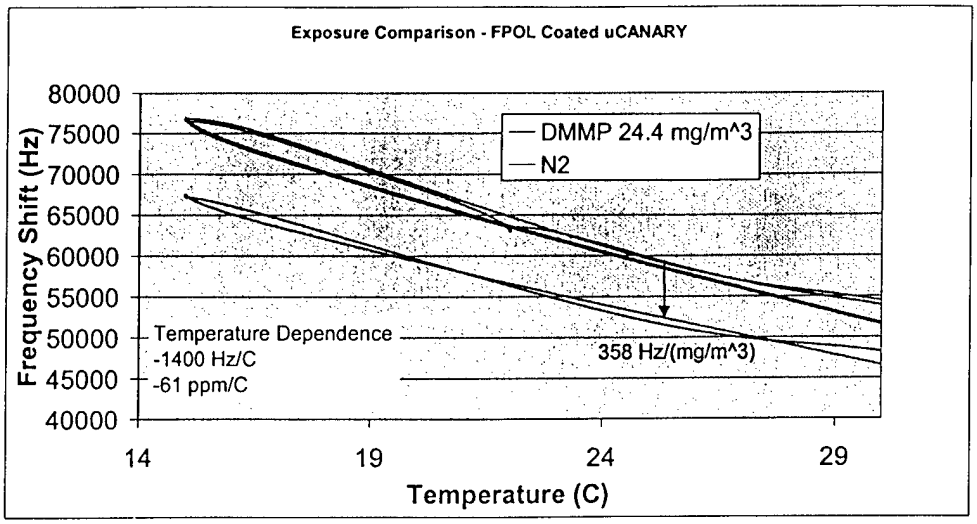
is shown that frequency decreases at a rate of approximately 1.5 kHz per degree Celsius with an increasing temperature. Temperature control is therefore important when conducting experiments using the CANARY. Two approaches can be taken into account for the temperature effect on sensor response. The first is to control the temperature of the sensor and the samples on the sensing surface. The second is to monitor the temperature of the sensor and scale the frequency reading accordingly. Both approaches could be implemented for the CANARY setup.



Figure

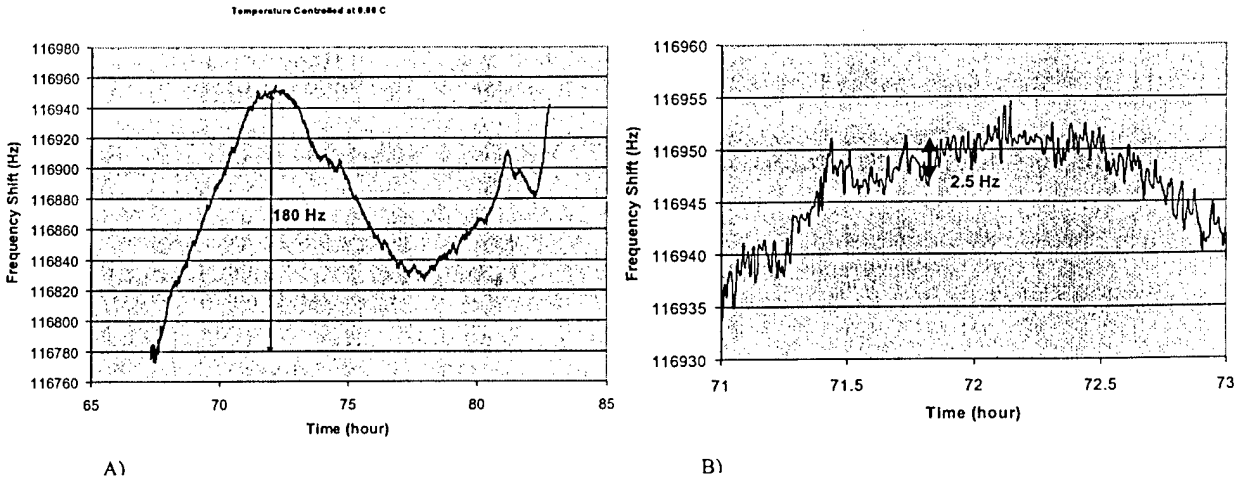
Effect of temperature variation on frequency output of a μCANARY device.

Temperature variation was found to be the largest contributor to measurement errors of frequency. Next, vapor exposure tests were conducted in which a polymer receptor coating for Sarin (nerve gas) was applied to the sensor. Using Sarin simulant for exposure, a detection limit of 19 parts-per-billion was measured (figure below).



Vapor exposure test of a μCANARY sensor with a polymer receptor coating that absorbs Sarin nerve agent. For this test, a Sarin simulant chemical, dimethyl-methlyphosphonate (DMMP) is used for the esosure. This test shows the variation in resonant frequency with temperature under exposed and unexposed conditions, and shows the reduction in resonant frequency that is obtained when the exposure occurs.

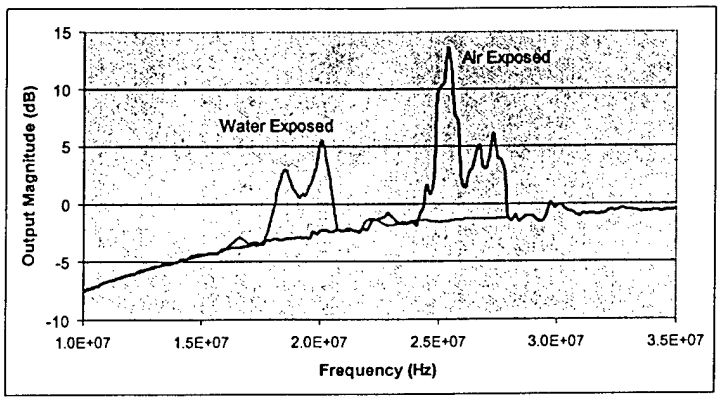
Under temperature controlled operation in air, the long term frequency drift and short-term frequency noise was characterized. Example plots of long term frequency stability and short-term frequency noise are shown in the figure below.



Figure

Characterization of (A) longer term frequency drift of a μCANARY sensor held at 0.0 C over a 17 hour period, and (B) characterization of short term frequency stability at a fixed temperature of 0.0 C. These measurements are used to determine overall frequency stability requirements and minimum detection

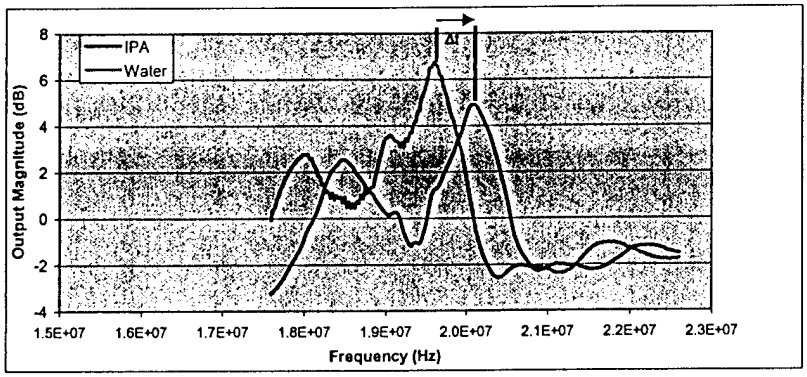
Next, operation of the sensor was characterized in liquid. The existence of resonant modes with fluid loading on the resonant membrane was confirmed. As shown in Figure below, a large reduction in resonant frequency is obtained when the sensor is loaded with a liquid.



Figure

Frequency shift induced when the sensor is exposed to a liquid. A large reduction infrequency is observed due to mass loading of the water on the membrane surface. In addition, a reduction inresonance magnitude and increase in mode width is observed.

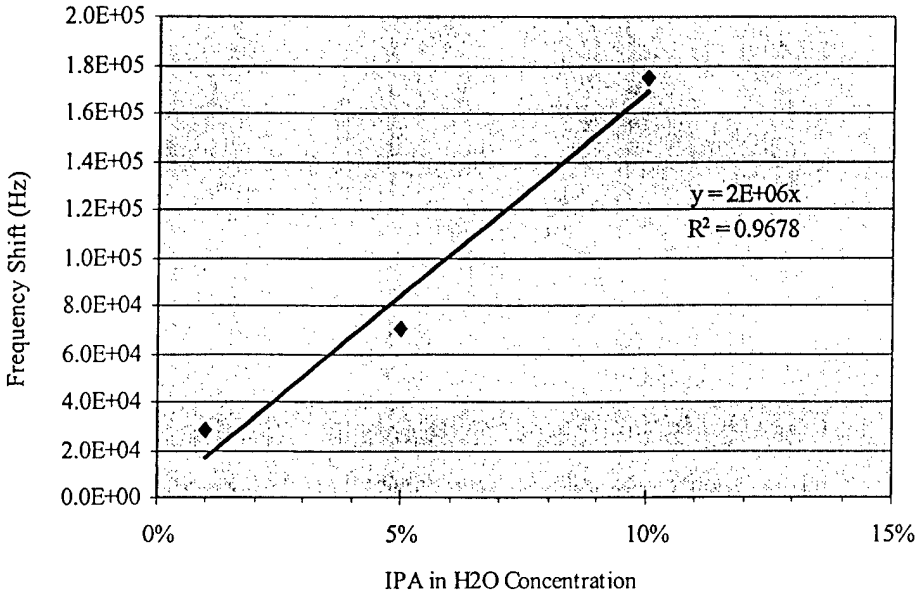
Next, an experiment was performed in which the sensor response to various mixtures of isopropanol (IPA) in water was measured. As shown in the figure below, a shift of the resonant modes is obtained when the sensor is exposed to IPA, corresponding to a change in the viscosity of the solution in contact with the sensor membrane.



Figure

Increase in resonant frequency observed when the sensor fluid is changed from water to IPA. The increased frequency corresponds to an decrease in liquid viscosity of IPA compared to water.

The figure below shows that a linear variation in fluid viscosity (using IPA/Water mixtures) results in a linear change in resonant frequency.



Figure

Correlation of MEMS sensor frequency shift and various concentrations of IPA. Linear correlation of frequency shift and concentration was obtained for isopropyl alcohol (IPA). The data were taken using a flow cell, open-loop setup at room temperature.

Plan: Our plans for the next year include: 1) Characterization of receptor coating application for Interleukins, 2) Characterization of exposure to laboratory samples, 3) Determination of the level of accuracy of the μCANARY sensor technique, and 4) Development of hardware and software for the microsensor system.

4.4 Simulation

In order to achieve a realistic, accurate, real-time medical simulation, several fundamental problems need to be solved, requiring the development of a set of modules (or components) that define the basic functionality of a simulator.

The approach chosen will emphasize the importance of tissue modeling and haptic feedback that will lead to the development of general organ models with realistic behavior. However, additional components have to be implemented in order to apply the result of research to the development of one or several simulator prototypes.

Progress: The various technological aspects of a simulator have been studied by the team members. Important elements that should be integrated into a surgical simulator have been identified. This step was fundamental to the process of developing a new technology.

Plan: From the identification of these elements and the findings based on extensive bibliographic research as well as the expertise of the team members/collaborators, the team will be able to identify: a) the complexity of each problem, b) its relevance in the development of a simulator, and c) a list of potential applications. Particular features are associated below with Specific Aims.

Specific Aim 1: Tissue modeling: Tissue modeling is probably the most complex problem in surgical simulation, and it covers both biomechanical testing of living tissues and real-time deformation of an organ.

- Tissue property measurement: development of a set of tools dedicated to the in vivo measurement of soft tissue characteristics. This work is done in collaboration with MIT.
- Deformable organ modeling: depending on the geometry, structure, and elastic properties of an organ. Four modeling classes for soft tissues have been distinguished:
- small deformations: relatively stiff organs under "small" forces (e.g. kidney, brain)
- large deformations: soft organs that can be easily deformed (e.g. intestine, liver, etc)
- solid organs: organs that can be assimilated to a solid body (e.g. liver, kidney, etc)
- hollow organs: organs composed of an elastic shell and internal fluid or gas (e.g. blood vessels, lungs, pancreas, intestinesetc)
- Soft tissue cutting: controls how the organ behaves during and after a resection.

Specific Aim 2: Haptics: Haptic rendering is a way to provide, through a mechanical interface, the sensation of touching a virtual object. The major steps towards the creation of a haptic feedback are:

- Haptic interface design
- Haptic interface controller
- Rigid instruments modeling (e.g. laparoscopic tools)
- Flexible tools modeling (e.g. catherters, flexible endoscopes)
- Real-time collision detection
- Tool/organ interactions

Specific Aim 3: Geometric modeling and visual feedback: Visual feedback is the process that allows recreating, on a computer monitor, the typical visual display associated with a specific category of procedures. This includes:

- 3D segmentation: how to extract a 3D surface of an organ from a CT or MR image
- Visible light rendering: a typical application would be open surgery
- Fluoroscopic rendering: by simulating x-ray images we can focus on endovascular surgery
- Endoscopic/laparoscopic view: this type of rendering is dedicated to laparoscopic surgery

Specific Aim 4: Physiology: Physiology is an important factor in surgical simulation. It is a way to describe the functional interactions between different organs as well as internal functionality of blood vessel, for instance.

- Fluid flow / pressure: representation of fluid characteristics at a macro level
- Pulsatile flow: detailed representation of specific flow characteristics
- Turbulent flow: detailed representation of specific flow characteristics

Specific Aim 5: Learning system: In order to turn the simulator into a teaching instrument, a learning system needs to be developed. This step is relatively dependent of the targeted application and therefore requires understanding the user domain.

Progress: Domain analysis: Most of the problem tasks identified previously in the Aims section are being tackled by researchers, mainly in the field of biomechanics, computer science, and robotics. What makes the development of a surgical simulator a real challenge is that every solution has to be computed in a fraction of a second: that is a major constraint. Because of this real-time constraint, trade-off between accuracy and computational speed is required. A rigorous domain analysis provided by the team members has allowed to understand the limitations of current simulators and what are the important research areas that have to be investigated in order to create better simulations.

Modules dependencies and system integration: The following diagrams describe the typical interactions and dependencies between the different elements of a simulator. Each component/module (figure below) can be seen as a black box that processes a set of inputs and produces a set of outputs.

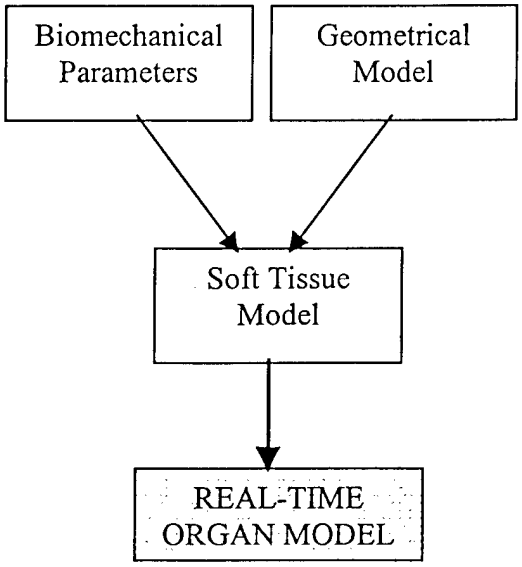


Figure – An example of input/output parameters for a simulation component.

The simulation engine (figure below) basically processes, synchronizes and controls the different modules in order to create the real-time simulation. The development of the real-time architecture is a very important step and the only way to put together the results of the fundamental research described above to produce a medical simulator.

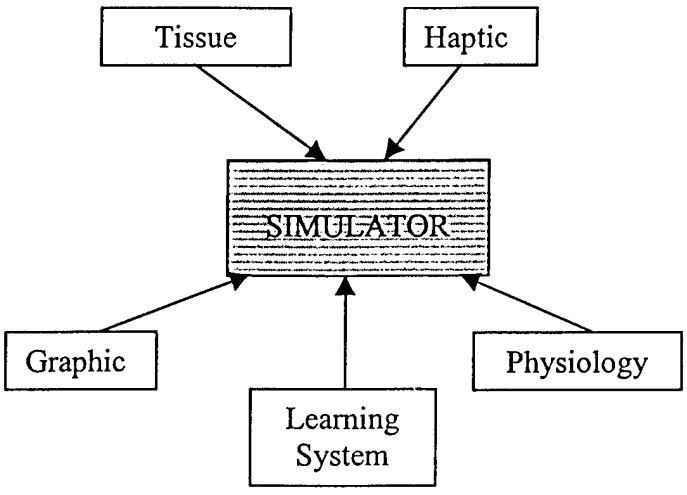


Figure – the simulator as a control and processing unit for a set of components.

4.5 Tissue Engineering

Task 1: Synthesize Vascularized Living Systems from the Platform of 2-D Silicon Microfabrication Technologies and Adapt to 3-Dimensional Living Devices

Progress: Since this work was based on a new concept and there had been no prior art, the first six months were aimed at designing experiments to test proof of principle. The fundamental idea was to use silicon microfabrication technologies to etch molds of an entire vascular supply from inlet artery to exchange capillaries to exit vein in two dimensions on a silicon wafer. The silicon was to be used as a mold to allow living vascular endothelial cells to form channels based on the mold. Then technologies were to be designed and tested to lift these living channels from the mold and to fold them into three-dimensional space. The appropriate parenchymal cell type could be added in steps during this process so that a complete vascularized new tissue could be formed in three-dimensional space. The work from 1.1 through 1.5 was performed in this time period. Silicon- and pyrex-based wafers were used. Etching techniques were developed for the purposes of channel formation. This included a branched array of channels similar in diameter to what was envisioned in the living tissue.

To date, hepatocytes have been successfully grown on silicon and pyrex, vascular endothelial cells on silicon and pyrex, and both have been lifted off the templates and folded into three-dimensional living tissues. Work has also been done on generating polymer films that can be used as a temporary fabric to help lift the living tissue from the device. Currently, the team is testing new configurations to successfully lift these living sheets off of the etched channels.

A second generation of design which now includes data related to the coronary circulation is now being etched. It should have the capacity to allow flow through the channels with and without living cells. A bioreactor has also been designed in which fluid flow can be achieved, tissue can be formed, and flow rates and pressures can be measured and changed.

Also, work with three-dimensional tissues has been performed in bioreactors as well as early animal implantation studies. Briefly, a three-dimensional bioreactor for hepatic growth has been designed and tested. A three-dimensional array of non-woven fibers has been used as a model for the scaffolding. Hepatocytes and endothelial cells have been added. Hepatocyte survival and function has been assessed using albumin secretion.

Living membranes of hepatocytes have been lifted from silicon wafers and implanted into the vascularized omentum of rats to model the potential organization of these structures in animals. The omentum is a well-vascularized thin fatty tissue that can be easily used as an implant site. The histology reveals good formation of sheets of hepatocytes with what appears to be early bile duct formation occurring spontaneously. There is good vascularization of the constructs as well. This tissue has been rolled into a three-dimensional architecture similar to a configuration that may be amendable for our silicon wafer technology.

Dr. Brian Cunningham has innovated layering etched polymer films to achieve the larger vascular inflows leading to the capillary bed and leading away through the venous system.

Plan:

1. Design and fabricate Silicon and Pyrex based systems providing an array of etched channels to act as a mold for generating a living network in 2 dimensions.
2. Design and test systems to allow lifting and folding of the vascularized tissue from the etched silicon mold.
3. Design bioreactors to house the device during tissue formation and folding.
4. Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters.
5. Investigate mechanisms of tissue development using molecular markers for gene developmental programs and programs of wound healing and regeneration.
6. Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device.

Development will continue for optimization and study from items 1 through 6. Data will be generated providing tissue organization, flow and pressure dynamics within the molds and modeling of new branching systems. Also, different designs will be added in to optimize lifting of the tissue intact and studying flow within the channels that is achieved. The multi-level laminate approach will be infolded to the design parameters. Also, the gene programs for normal hepatic development have been infolded into the study and will then be studied for normal morphogenesis and neomorphogenesis of new tissue in this array and in the three-dimensional arrays.

Toward the end of the year, if the system has been sufficiently optimized, early implant studies with vascularization in place can begin.

Task 2: Synthesize Vascularized Living Systems from the Platform of 3-D Printing Technology

Progress: Work to date in this area is mostly organizational. Multiple meetings with Dr. Griffith's group at MIT and Therics which has licensed the three-dimensional printing technology from MIT have occurred. Therics has agreed to build a complete machine in Dr. Griffith's lab at MIT for the sole purpose of tissue engineering. The team will be able to access that machine for the purpose of creating vascularized tissue. It should be complete by the end of September, 1999. To model three-dimensional systems, we have performed a series of experiments have been performed in which vascular casts for the heart and liver have been generated. These casts have been completed through the level of the capillaries and back to the veins.

Plan: Currently, the team is testing various imaging modalities to attempt to get these three-dimensional vascular casts into digital information in the computer. The plan is to then understand the fractal nature of these systems which can then help us in the design of the three-dimensional channel arrays, the three-dimensional printing polymer, as well as conversion to the two-dimensional systems for the silicon technology.

Dr. Griffith's group is focused on studying and changing the surface chemistry of polymer arrays for the purposes of cell signaling and new tissue generation. This work will be infolded into the three-dimensional printing technology.

Bioreactor development in three-dimensions using random arrays of polymer fibers, hepatocytes, and endothelial cells has been achieved. Albumin production has been studied and found to increase over a three-week interval.

A new approach based on the vascular casting technique has been conceived of, disclosed as a potential patent, and tested. Briefly, gallium metal melts at room temperature. It can be used either in the two-dimensional etched molds or in the three-dimensional vascular circulation of an organ to produce an accurate vascular cast of gallium metal as a solid. This solid then can be placed within degradable polymer as a liquid or spray. When the polymer has solidified, the temperature can be raised allowing the gallium to flow from it. This then would give us the vascular circulation including the capillaries embedded as channels within a degradable polymer matri4. To date, gallium casts have been made from the coronary circulation. The team is now applying degradable polymer to it to generate the vascular channels in polymer. A patent disclosure has been written for this as well.

Plan:

1. Optimize the design of 3-D polymer systems with an internal tubular branching architecture based on the flow and pressure dynamics of rat liver and rat skeletal muscle.
2. Optimize the design and fabricate in vitro flow bioreactors to generate vascularized liver and skeletal tissue which permit their analysis. Develop assays to study the generation of tissue and its histologic, biomechanical, and biochemical parameters.
3. Compare the generation of new tissue using this technique to A1.
4. Investigate mechanisms of tissue development using molecular markers for genetic developmental programs and programs of wound healing and regeneration.
5. Begin animal implantation studies to begin to understand perfusion, survival, and function of the living device.

These systems will include not only the three-dimensional printing technology but also the gallium technology and angiogenesis generation. Tissues studied have been broadened to include liver, heart, and kidney. Also, implant studies of intestine as another vital organ are underway using angiogenesis as the fundamental approach. At the end of this year, a model- channeled system patterned on the three-dimensional printer should be available and tissue morphogenesis in a bioreactor will have been studied. Likewise, proof of concept for the gallium technology should have been demonstrated. If the data supports ongoing work in this area, it will then produce polymer devices which can be seeded with vascular endothelial cells and studied in vitro in bioreactors. If very successful, early implantation studies into animals may be achieved.

5.0 CONCLUSION

During the first year of DoD funding, CIMIT has established Clinical Focus Areas with promising research in cardiovascular disease, cancer, stroke and trauma & critical care and has provided a mechanism, the New Initiatives CFA, to identify and foster the integration new avenues of research. Although clinically driven, CIMIT has identified sophisticated technical capabilities and new enabling technologies through its Advanced Technology Teams. The expanded ATTs work closely and synergistically with clinical investigators in specific subprojects to achieve the stated goals of the research. The breath and depth of interactions between clinicians, clinical researchers and technical scientists is a unique strength of the CIMIT proposal that should lead to significant progress in new minimally invasive diagnostic and therapeutic techniques. The technology assessment and outcomes component has expanded from an ATT to a critical program for all CIMIT research. The ATT program provides an infrastructure and the expertise to properly evaluate minimally invasive diagnostic and therapeutic procedures at all stages of development, particularly during the early stages from discovery to preliminary clinical testing, when extensive data regarding clinical effectiveness may not yet be available.

Progress during year 1 has been significant in many areas including the development and application of novel techniques (optical and microwave) to detect early hemorrhage in vivo, development of innovative techniques to diagnosis and treat acute stroke, fabrication of MEMS devices for assessing MOF and novel approached for tissue engineering. With continued DOD support, CIMIT is well positioned to take the leading role in defining the future of minimally invasive health care for the nation. A superb team of clinicians, scientists, and researchers are assembled and poised to take the next leap forward in providing higher quality care to both military personnel and the civilian population. CIMIT will focus on conceiving, developing, reducing-to-practice and evaluating innovative technologies and procedures. The combined resources of the Government-Industry-Academia-Hospital collaborations and the DOD personnel training and exchange programs provide a superlative network of technological capability. The resulting innovations will certainly produce cost effective, minimally invasive and maximally effective healthcare.

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7.0 APPENDICES

APPENDIX A: CIMIT EDUCATION PROGRAM

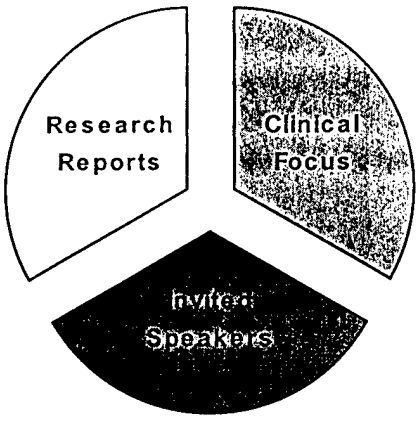
The scope of the CIMIT Education Program includes informing the CIMIT community attracting and educating academic and military investigators in the field of minimally invasive therapy research and practice, and interacting with world leaders involved in active minimally invasive therapy programs. CIMIT interprets "education" in its most expansive form. The goal is to establish a world-class program that encompasses CIMIT consortium members and DoD collaborators. Using a multi-faceted approach, the program functions as an internal resource, an external point of contact, and a focus for public outreach.

The CIMIT Education Program has made significant advances in the past year having learned from the first year's research and program development and is adapting its goals, research, and year two implementation plan accordingly.

CIMIT FORUM: The original concept for the CIMIT Education Program was to plan a series of lectures, discussions, and work groups that would highlight the most advanced devices and techniques currently available in minimally invasive diagnosis and therapy. Sessions included:

- **Clinical Focus Sessions:**

  An internal presentation series designed to give a broad report of the current state-of-clinical practice from Partners' and DoD physicians. Sessions take place during regularly scheduled CIMIT meetings and are designed to permit lengthy exchange between the speakers and the CIMIT faculty. Physicians presenting at these sessions are asked to discuss particular techniques within their practice, emphasizing technology barriers that represent boundaries to further innovation. Through the ensuing interdisciplinary discussion with CIMIT's engineers, scientists and physicians, and industrial partners, likely avenues for cooperative problem solving can be identified.

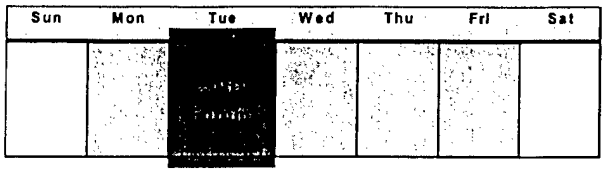


- **Invited Speakers**

  The Education Program augments CIMIT's overall program through a series of invited speakers chosen to target specific areas that complement the CFA's or ATT's. Physicians and scientists present one-hour lectures focussed on cutting edge procedures and technologies which are outside of CIMIT's current programs.

Research Reports

This internal presentation series is designed to give CIMIT investigators an opportunity to discuss ongoing as well as proposed in an interdisciplinary environment for review, feedback, and collaborative discussion. Reports include progress reports from CFA and ATT programs as well as proposals from potential collaborators at other institutions.



These three different but complementary formats for discussion and collaboration have been combined into a weekly meeting series now known as the CIMIT Forum. The CIMIT Forum is an open conference for CIMIT members, medical and academic partners, industry, and other interested parties to meet, hear reports of ground-breaking research in minimally invasive therapy, and discuss implications, extensions, and implementation of research results.

Summaries of the meetings are recorded and available to interested parties on the CIMIT web site [www.cimit.org]. To date, over 100 presentations have been heard as part of the CIMIT Forum Series by a dedicated audience of 40-60 core members.

SAMPLE TOPICS FROM CIMIT FORUM

Laparoscopic Surgery: The Good, the Bad, and the Ugly

Jonathan M. Sackier, M.D., F.R.C.S., F.A.C.S. Professor of Surgery Director of the Washington Institute for Surgical Endoscopy The George Washington University Medical Center

The first speaker in the CIMIT Lecture Series, Jonathan Sackier, M.D., George Washington University, presented on "Minimally Invasive Therapy: The Good, The Bad and The Ugly," a humorous and pointed survey of the development of and current issues in minimally invasive therapy. A sampling of topics included: Cost of new technology; Using laparoscopic diagnosis to avoid unnecessary surgery; Oscillations from quackery, to overuse, to banning of procedures, to reasonable implementation which have governed the introduction of minimally invasive therapies; Ending the turf battles; Using robots for "predictable, boring jobs"; Questioning the value of telemedicine as a use of resources; Simulating skill sets for educational purposes.

Collaboration and Innovation in the Development of Minimally Invasive Therapies: The Oslo Approach

Erik Fosse, M.D., PhD. Frode Laerum, M.D., Ph.D., MHA Jan Svennevig, M.D. The Interventional Centre at Rikshospitalet Oslo, Norway

Robotic Cardiac Surgery

Michael J. Mack, M.D. Chairman Cardiopulmonary Research Science and Technology Institute Clinical Assistant Professor Department of Thoracic Surgery University of Texas Southwestern Medical School at Dallas

Clinical Applications of Fetal Diagnosis and Therapy

N. Scott Adzick, M.D. Surgeon-in-Chief The Children's Hospital of Pennsylvania

Dr. Scott Adzick discussed Clinical Applications of Fetal Diagnosis and Therapy. The ability to detect fetal abnormalities has led to the development of a number of in utero treatments. Some of these are motivated by the fact that certain fetal abnormalities can damage the mother; others are motivated by the ability to treat and cure in utero abnormalities that are much more severe if the fetus is allowed to go to term. Examples of treatment include management of obstruction of the fetal airway by performing a cesarean section, operating to control the obstruction and returning the fetus to womb. Another treatment is designed to avoid neurological deficits arising from exposure of the spinal cord to uterine fluid; Alloderm has been used to close these defects. Among the tools used in these procedures are fast MRI techniques which allow well-resolved images of the fetus to be obtained in times too short to allow blurring by fetal motion. These MRI images have been used to detect abnormal growths such as lung lesions, which can compress the esophagus, lungs and other organs. The group is starting to perform in-utero hematopoietic stem cell transplants, taking advantage of the fact that there is immunologic tolerance in early development. Overall, a major trend in pediatric surgery has been earlier and earlier interventions, including fetal surgery. A major need for development of the field is development of new diagnostic and therapeutic endoscopes for fetal use. Other needs include fetal monitoring probes for pH and IUP, delivery systems for stem cell and gene therapy treatments, and contrast agents for use with US and MR imaging.

Fibroid Embolization: A Model for New Procedure Development

Michael Pentecost, M.D. Professor and Chairman Department of Radiology Georgetown University Hospital

Mike Pentecost, MD from Georgetown University discussed the use of fibroid embolization as an alternative to hysterectomy. The new procedure is motivated in part by the fact that 175 to 200K hysterectomies are performed annually to eliminate fibroids. The procedure involved the introduction of a small (5F) catheter into both uterine arteries and injecting polyvinyl particles, which lead to devascularization of the fibroid and its ultimate shrinkage. The procedure has the advantage of having over 90% of the patients discharged on the same day or with a one-night stay. Issues for further investigation include long-term effects, especially with respect to fertility.

Endometrial Ablation Techniques: Treatment Choices in the New Millenium

Olav Istre, M.D., Ph.D. Consultant, Gynaecology Obstetric Department The University of Oslo, Aker Hospital Oslo, Norway

Dr. Istre discussed the European perspective in patient choices, treatment choices, and risks involved with methods of treating dysfunctional uterine bleeding.

E-DUCATION

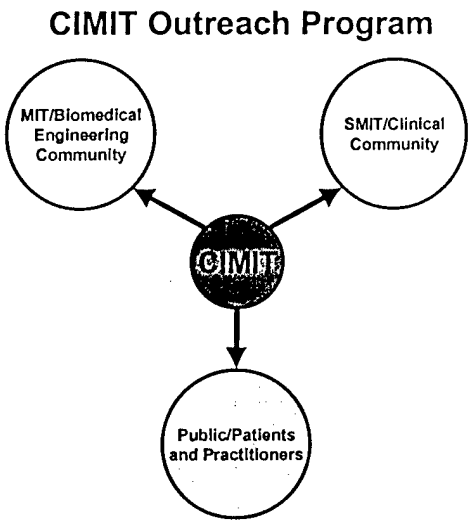
One of CIMIT's founding goals has been to leverage the ability of the Internet to serve as an educational tool, a center of communication and a resource for public interaction. The current website [www.cimit.org] has been significantly expanded over the past year to allow patients to learn about minimally invasive techniques. Sample topics include hiatal hernia surgery, laparoscopic donor nephrectomy, tumor ablation, hysteroscopy, stroke diagnosis and treatment, and aortic aneurysm repair.

The site's intranet allows secure access to internal communications, administrative updates, shared databases, conference announcements, grants progress, DoD interaction and corporate collaborations for consortium members. As satellite centers are brought into CIMIT, the intranet will also serve as a communications platform between faculty at the different institutions, both civilian and military.

OUTREACH

The CIMIT Outreach Program has Three main components, each of which has made major strides in the past year:

- **The CIMIT Symposia at Massachusetts Institute of Technology**



CIMIT faculty presented clinical problem sessions at MIT under the auspices of the Harvard/MIT Health Sciences Technology Program (HST), with the assistance of the Co-Directors of HST Program, Martha Gray, Ph.D. and Joseph Bonventre, M.D., Ph.D. The goal of these sessions has been to open a dialogue between the engineering capabilities at MIT and the clinical expertise in the consortium hospitals. The hope is to engage MIT students in an ongoing relationship with clinical medicine as a whole and CIMIT in particular by presenting real-world clinical examples and the obstacles encountered which prevent clinical innovation.

- **Scientific Outreach**

CIMIT hosted the 11th Annual SMIT/CIMIT International Congress at the Westin Copley Place, September 16-18, 1999. This will be followed by semi-annual scientific meetings which will focus on single topics in detail. The goal of this series is to establish CIMIT as a national resource for state-of-the-art exchange on enabling technologies and clinical progress. These in-depth symposia will be scheduled at different venues locally, at the DOD, at satellite centers and other appropriate sites. Proceedings of the symposia will be offered for publication as a supplement to peer-reviewed journals.

- **Communications Program**

CIMIT has designed a communications program to address its diverse communication needs, audiences, and resources. Key objectives include: educating researchers and clinicians about the potential of minimally invasive therapy, establishing CIMIT as the

preeminent resource on minimally invasive therapy, and positioning Partners institutions as the leading clinical sites for minimally invasive therapy.

To date, the cornerstone of the program has been a communications coordinator from the public relations firm of Agnew, Carter, McCarthy. Work to date has included: developing an information kit to accommodate a variety of media and audiences; identifying and training media spokespeople; developing and maintaining a segmented and targeted media database; and coordinating a quarterly "news brief" containing highlights of CIMIT news, activities, and industry developments.

- **DOD Fellowship Program**

In year two, CIMIT will confer with the DoD to determine the feasibility of a Fellowship program for military physicians and scientists. The program is envisioned to provide research training in one or several of the disciplines associated with minimally invasive techniques that have particular relevance to the military, and may require TDY and salary support by the sponsoring agency. Trainees could choose to have their educational experience at an appropriate DOD or CIMIT site.

- **Metrics**

CIMIT participated in the SPIE Aerosense '99 Conference in Orlando, hosting a session on Battlefield Medical Technologies. Several papers from nationally recognized authors, both civilian and military, were presented in this session, including a scientific report of the simulation based educational efforts led by CIMIT's Co-Director of Educational Programs, Dr. David Williamson Shaffer [Shaffer, DW, Meglan, D, Ferrell, M, Dawson, S (1999). "Virtual Rounds: simulation-based education in procedural medicine." In Pien, H (Ed.), Proceedings of SPIE Vol. 3712: Battlefield Biomedical Technologies.] Based upon the success of this seminar, CIMIT will host the Battlefield Medical Technologies session at SPIE 2000.

In September, 1999, CIMIT co-hosted the Annual Meeting of the Society for Minimally Invasive Therapy (SMIT), a forum attended by 400 leading researchers and clinicians in the field of minimally invasive therapies from around the world. The program included a number of plenary and scientific paper sessions on work sponsored by CIMIT. (See following pages for summary of the scientific program.)

Research and Clinical Presentations at SMIT/CIMIT Conference

Brian T. Cunningham, PhD
In-Vivo Biosensors for Minimally Invasive Therapy

Bruce A. McKinley, PhD
Sensors for Tissue Monitoring and Use in Intensive Care

Hermann Reichenspurner, MD, PhD
The Use of Robotic Instrumentation for Endoscopic Coronary Artery Bypass Grafting

Michael J. Mack, MD
The Future of Surgical Augmentation

G. Scott Gazelle, MD, MPH, PhD Milton C. Weinstein, PhD
Technology Assessment and Cost Effectiveness Analysis: Issues and Challenges

Gary J. Tearney, PhD, MD
Clinical Applications of Optical Coherence Tomography

Mary-Ann Mycek, PhD
Laser Spectroscopy for Endoscopic Pre-Cancer Detection

Synthesizing Donor Organs and Revolutionizing Drug Therapy

Joseph P. Vacanti, MD
The Clinical Implications of Tissue Engineering

Robert S. Langer, ScD
Biodegradable Polymers and Drug Delivery

Ferenc A. Jolesz, MD

Interventional and Intraoperative MR Imaging

Kullervo Hynynen, PhD
Focused Ultrasound

G. Rees Cosgrove, MD
Interstitial Radiosurgery: The Photon Radiosurgical System

David W. Shaffer, MS, PhD
Computer-based Curriculum Development

Dwight Meglan, PhD
Simulation-based Surgery Training

Jeffrey B. Cooper, PhD
Realistic Patient Simulation

Desmond H. Birkett, MD
Ethics of Telemedicine

Paul R. Heinerscheid, MBA MSC
Applications of Institutional Video Networks in Medical Training

Lawrence H. Cohn, MD
Minimally Invasive Valve Repair and Replacement

Robert Emery, MD
MI-CABG

Stephen N. Oesterle, MD
New Approaches and Conduits: In-Situ Venous Arterialization and Coronary Artery Bypass

Ralph J. Damiano, MD
Computer-Assisted Coronary Bypass Grafting: An Enabling Technology for Endoscopic Microsurgery

Erik Fosse, MD, PhD
Integrating Image Guidance into the Cardiac O.R.

Nicolaus J. Reifart, MD
Coronary Stenting: A European View

John A. Kaufman, MD
Abdominal Aortic Stent-Grafts

Gary Roubin, MD, PhD, FACC, FRACP
Carotid Stenting: Current Techniques and Results

Michael L. J. Apuzzo, MD
Neurosurgery as a Paradigm for Minimally Invasive Techniques

Peter M. Black, MD, PhD
Image-Guided Neurosurgery Including the Intraoperative MRI

L. Nelson Hopkins, MD
Endovascular Approach to Revascularization in the Central Nervous System

James Burke
The John Wickham Lecture: "Innovation, Serendipity, and Healing"

Robert G. Forman, MD, FRCOG
Fibroids and Fertility

Nicole D. Ciraru-Vigneron, MD
Arterial Embolization of Uterine Myomata: Results of a 7-year Study at Hospital Lariboisiere

Jacques Ravina, MD
Place of Arterial Embolization in the Treatment of Uterine Myomata in Young Women

Bruce McLucas, MD
Predictive Factors for Success in Uterine Fibroid Embolization

A. Aymard, MD
Angiographic Aspects and Incidents on Uterine Embolization

John F. Reidy, MD
Uterine Artery Embolization for Fibroid Disease

Robert L. Worthington-Kirsch, MD
Anatomic Variants in Uterine Artery Embolization: Recognition and Management

Harold A. Mitty, MD
Uterine Artery Embolization of Myomas: Preliminary Results of Gelatin Sponge Pledgets as the Embolic Agent

Elliot B. Levy, MD
Two Catheter Technique for Embolization in the Treatment of Symptomatic Uterine Leiomyomata

Arnold Rappoport, MD
Uterine Artery Embolization in an Outpatient Surgery Center, Using a Mobile C-Arm Fluoroscopy Unit

Woodruff J. Walker, MD, MB, BS, FRCR, FFR(SA)
Uterine Artery Embolization for Myomata: Guildford Series Results, Complications, and Failures

Lloyd E. Ratner, MD
Transplantation

Namir Katkhouda, MD, FACS
Applications of Fibrin Sealant in Minimally Invasive Surgery

Gerhard F. Buess, MD
Colo-rectal Endoluminal Microsurgery

Keith B. Isaacson, MD
Endometrial Ablation

John F. Reidy, MD
Uterine Artery Embolization - Early Results and Complications

Grace M. Janik, MD, FACOG
Tubal Reanastamosis

John C. Wain, MD
Thoracic Minimally Invasive Surgery

Cameron Wright, MD
Minimally Invasive Thoracic Surgery: Now and in the Future

Robert J. Caccavale, MD
Is Video-Assisted Thoracic Surgery Superior to Traditional Thoracotomy?

Harald Fischer, PhD
Manipulator for Simultaneous Imaging/Biopsy/Therapy of Breast Lesions in a High-Field Whole-Body MR-Scanner

Delphine C. Germain, MSc
MR Temperature Mapping to Monitor Laser Ablations in the Liver and the Breast

Krishna Moorthy
Minimally Invasive Staging Procedure in Carcinoma Breast - Use of Frozen Section Examination

Peter N. Swischuk
Dosimetry, Ultrasound and Histopathologic Correlation of Laser Induced Thermotherapy of Renal Cell Carcinoma in Man

Irene Georgakoudi, PhD
Endoscopic Detection of Dysplasia in Patients with Barrett's Esophagus Using Light-Scattering Spectroscopy

Rainer Seibel, MD
Comparison of Tomographic-Guided Interventions

Rainer Seibel, MD
Feasibility of Electron Beam-CT-Guided and Comparison with CT-Guided Interventions

Andreas Melzer
Simulation of Moving Artifacts in Magnetic Resonance Imaging

Constantin Cope, MD
Peroral Creation of Gastroenteric Anastomoses
Mubin I. Syed, MD
Direct Percutaneous Jejunostomy for Feeding in the Postoperative Patient

Barry Daly
Methods of Needle Placement for Percutaneous Interventions Utilizing CT Fluoroscopy Guidance: Experience in 381 Patients

Peter G. Chait
Transcatheter Management of Intrahepatic IVC Interruption by Means of Perforation, Dilation and Stent Placement

Horacio R. D'Agostino
Safety and Efficacy of Percutaneous Catheter Manipulations and Videoendoscopy for Evacuation of Necrotic Debris from Pancreatic Fluid Collections

William R. Lees
Image Guided Thermal Ablation of Colorectal Liver Metastases, Time for a Randomised, Controlled Trial Versus Hepatic Resection

Peter G. Chait
A New Technique for the Management of Severe Takayasu's Disease Involving Both Renal Arteries

Kevin R. Cleary
Minimally Invasive Spine Procedures: Mobile CT and 3D Visualization for Percutaneous Vertebroplasty

Andreas Melzer, MD, DDS
Technique of Percutaneous Laser Nucleotomy of Lumbar Intervertebral Disk Herniation Under MRI-Control (MRPLNT)

Minoru Matsuda, MD, PhD
Hand-Assisted Laparoscopic Distal Gastrectomy for Early Gastric Cancer

Joshua I. S. Bleler
Hand-Assisted Laparoscopy: Early Results with Vertical Banded Gastroplasty

Marina S. Kurian, MD
Hand-Assisted Laparoscopic Donor Hepatectomy in a Porcine Model

Robert Frese, MD
Laparoscopy in Renal Transplant Patients: Standards and Specifics

Brent D. Matthews, MD
Laparoscopic Adrenalectomy for Metastases

Michael E. Moran, MD
Ultasonic Dissection During Laparoscopic Nephrectomy and Adrenalectomy

Michael E. Moran, MD
Tissue Removal Utilizing the Steiner MorcellatorTM Within a LapsacTM: Effect of a Fluid Filled Environment

Paresh Shah, MD
Peritoneal pH During Laparoscopy is Dependent on Ambient Gas Environment: Helium and Nitrous Oxide Do Not Cause Peritoneal Acidosis

Randy S. Haluck, MD
Port-Less Laparoscopic Instruments

Akiteru Hayashi
Endoscopically Assisted Repair of Facial Bone Fractures

Barry Daly
Trochar and Port Site Herniae After Laparoscopic Surgery: Imaging Diagnosis

W. Peter Geis, MD
The Safest Approach to Laparoscopic Cholecystectomy: Humanism and Technology

Sajid Mahmud
The Significance of Cystic Duct Stones Encountered During Laparoscopic Cholecystectomy

Ahmad H. M. Nassar
The Management of Suspected Ductal Stones. A Limited Role for ERCP.

Cornelis A. Grimbergen, PhD, MSc
Comparing Minimally Invasive and Open Surgery Using Time-Motion Analysis

Abdullah D. Aldohayan
Comparison Between Laparoscopic Splenectomy and Hand Assisted Laparoscopic Splenectomy

Abdullah D. Aldohayan
Laparoscopic Percutaneous Closure of Deep Inguinal Ring in Indirect Inguinal Hernia

Abdullah D. Aldohayan
Laparoscopic Port Closure Using Special Needle, A Simple Economic, Easy Technique

Alberto Arezzo, MD
Robotic Optic Positioning Systems for Solo Surgery. An Experimental Randomized Trial.

Alberto Arezzo, MD
A New Endoscopic Hemostasic Device. Evaluation and Comparison with Ultrasonic Dissectors.

Alberto Arezzo, MD
The Tuebingen Balloon. First Clinical Results of a New Technique for the Calibration of the Nissen Fundoplication.

Alberto Arezzo, MD
The Shadow Telescope. A Telescope with Optimised Illumination.

Jonathan M. Gilbert
The 'Endoassist' Robotic Camera Holder Abolishes the Need for a Human Assistant in Laparoscopic Cholecystectomy

Manfred Y. Selig
Voice Controlled Camera Guiding System Felix for Endoscopic Cardiac Surgery

Hans F.L. Goosen
Integrated Multiple Blood Parameter Sensor for Use in a Catheter

Andy Black
Planning Significant Projects within the Health Sector

Richard A. Jorgensen, MD
Using the Internet for Data Collection and Retrieval

Timothy A. Rockall
Clinical Use of the Ligasure TM Vessel Sealing System in Colonic Surgery

Andreas Melzer, MD, DDS
Prototype of a New Stent with Interactive Magnetic Resonance Signal Intensity

Andreas Melzer, MD, DDS
Technique of MRI Controlled Neuro-Endoscopic Procedures

Andreas Melzer, MD, DDS
Experimental Laparo-Endoscopic Surgery in Combination with Magnetic Resonance Imaging

Iris B. Brune, MD
Laparoscopic or Open Surgery: The Role of Postoperative Immunosuppression in the Choice of Surgical Access

Roman Th. Carbon
Biomaterials in MIS: Evaluation of Surface Strength and Drug Delivery

Roman Th. Carbon
Tissue Management in MIS with Collagen and Tissue Glue

Christian Tuerk
Etiology-Dependent Clinical Analysis of Extracorporeal Shock Wave Treatment of Pseudarthrosis

Christian Doehn
Laparoscopic Treatment of Posttransplant Lymphoceles

Christian Doehn
Operative and Longterm Results of Laparoscopic Nephropexy

Christian Doehn

Lithiasis of the Renal Allograft

Amiel Gilad
Bone Anchored Sling for the Treatment of Postprostatectomy Incontinence

Amiel Gilad
A New Minimally Invasive Pubovaginal Sling Procedure Using a Bone Anchoring Device for the Treatment of Stress Urinary Incontinence

Amiel Gilad
Artificial Neural Network in the Workup of Female Urinary Incontinence: Is Urodynamic Investigation Really Needed

Maurice St. Michel, MD
Acustic Energy: New Therapeutic Aspects in Urology

Maurice St. Michel, MD
First Clinical Datas About Urological Application of Modulith SLK. - A Lithotriptor for Interdisciplinary Use

Maurice St. Michel, MD
Clinical Evaluation of Interactive Navigation System for Integration of Fluoroscopic and Ultrasound Imaging of the Modulith SLK Lithotripter

Senthil Nathan
Magnetic Resonance Imaging of Periurethral Macroplastique

Paolo Beltrami
Comparison Between Percutaneous (PCNL) and Extracorporeal (ESWL) Treatment in Simple Renal Calculosis

Jared Torkington
Learning Curves and Learning Effects - Using a Virtual Reality Simulator to Assess Laparoscopic Skill

Jared Torkington
Is an Aptitude for Mental Imagery Predictive of Laparoscopic Skill?

Timothy J. Brown
Comparing Laparoscopic Skill in Surgical and Gynaecological Trainees Attending Basic Skills Training Courses Utilizing Virtual Reality and Physical Simulations.

Timothy J. Brown
A Novel Objective Method for Assessing Surgical Dexterity - Straight from the Hands of Behavioural Psychologists

Simon G. T. Smith
Objective Evaluation of Laparoscopic Dexterity Performing Simulated Laparoscopic Cholecystectomy

Simon G. T. Smith
Movement Analysis Using Electromagnetic Trackers - An Objective Training and Assessment Tool for Surgeons

Anthony G. Gallagher
Psychomotor Skills Assessment of Experienced, Junior and Novice Laparoscopists with Virtual Reality

Anthony G. Gallagher
Traditional and 'Virtual Reality' Training in Laparoscopic Skill Acquisition; A Case Control Comparison

Robrecht Ceulemans, MD
Virtual Reality Does Not Predict the Endoscopic Performance of Novice Surgeons

Richard M. Satava, MD
Current Trends in Surgical Simulation Using Virtual Reality

Karen T. den Boer, MD
Learning of Diagnostic Laparoscopic Skills

Christopher T. Ducko
The Benefits of a Three-Dimensional Video System in Robotically-Assisted Endoscopic Surgery

Luis A. Sanchez
The Use of the Minimally Invasive Endopath System for Reversed and Insitu Lower Extremity Arterial Reconstructions

Bernd Vogel
ENDOSTAB: An Endoscopic Pressure Stabilizer for the Vascular Section to be Anastomosed in Minimally Invasive Cardiosurgery

Friedrich Christian Riess
Hybrid Revascularization: Promising Alternative for Conventional Coronary Bypass Operation

Randall K. Wolf
Totally Robotic Thorascopic Internal Thoracic Artery Mobilization

Abdullah D. Aldohayan
Transaxillary Thorascopic Sympathectomy Experience in Hot Climate: Management of the Dominant Hand

Abdullah D. Aldohayan
Thoroscopic Sympathectomy and Highly Selective Thorascopic Sympathectomy

Gary P. Siskin
The Feasibility of Outpatient Uterine Artery Embolization as Treatment for Symptomatic Uterine Fibroids

Fred Burbank, MD
A New Alternative to Uterine Artery Embolization

Robert T. Andrews, MD
Radiation Exposure for Patients Undergoing Uterine Artery Embolization

Rodolfo Lanocita
A Fatal Complication of Percutaneous Embolization for Treatment of Uterine Fibroids

Anthony A. Nicholson
Fibroid Embolization: Observations in 24 Patients

Gaylene E. Pron
Uterine Artery Embolization for Symptomatic Fibroids: Treatment Complications, Recovery and Satisfaction of Women Participating in a Multi-Center Clinical Trial

Martin E. Simons, MD, FRCPC
Technique Preferences and Short-Term Success in a Multi-Center Clinical Trial of Uterine Artery Embolization for Fibroids

Gaylene E. Pron
Uterine Artery Embolization for Symptomatic Fibroids: Sarcoma, Pregnancy and Other Reasons for Treatment Relapse or Failure

Carlos G. Forcade, MD
No Interventional Radiologist is an Island

Francis L. Hutchins, Jr., MD
Selective Uterine Artery Embolization as Primary Treatment for Symptomatic Leiomyomata Uteri: A Review of 305 Consecutive Cases

Elliot B. Levy, MD
Registration of Digital Subtraction Angiography Images in Uterine Fibroid Embolization

Robert L. Worthington-Kirsch, MD
Time Course of Pain after Uterine Artery Embolization for Fibroid Disease

In June, 1999, CIMIT proposed a new project in Advanced Medical Simulation to the Combat Casualty Care command. Funding for this peer-reviewed project was approved and work on developing basic simulation science has begun. These efforts are discussed elsewhere in this report.

Plan: In the coming year, the CIMIT Education Program will continue to build on the successes of the previous year by improving current program offerings and developing new innovative approaches to education, outreach, and training in the field of minimally invasive therapy.

CIMIT has recently hired a Co-Director of Education, Dr. David Shaffer, who has a background in education and technology-based training. The new Co-Director will work jointly with the existing Director of Education, Dr. Steven Dawson, to develop a robust educational program for CIMIT guided by sound pedagogical principles as well as the clinical and technical needs of the CIMIT program membership.

CIMIT Forum: The Forum series will continue to include invited speakers, research presentations, and clinical focus sessions. Proposed revisions to the Forum format include the addition of a CIMIT host and moderator for invited speakers, as well as a panel of discussants for topics presented. Specific guidelines for hosts, discussants, and speakers, designed to generate more in-depth discussion of topics are being designed and will be implemented and developed through a trial basis in the Fall of 1999 and spring of 2000.

Website: There are plans to continue refining and expanding the CIMIT website during the coming year. A new version of the website was released over the summer, but needs further development in terms of both technical and internal infrastructure. The goal is to streamline the processes through which timely information from the CIMIT research community and the field of minimally invasive therapy is collected and updated. There are also plans to revise the technical infrastructure for web support, making the site easier to maintain and update. The goal of both of these changes is to make the website a more effective communications and outreach tool.

There are plans to hire a Director of Communications for CIMIT who will continue the work of developing a communications and media relations program as outlined in our original proposal, and as implemented in the first phase by the media firm of Agnew, Carter, and McCarthy. Duties of the Director of Communications will include educating researchers and clinicians about the potential of minimally invasive therapy, establishing CIMIT as the preeminent resource on minimally invasive therapy, and positioning Partners institutions as the leading clinical sites for minimally invasive therapy.

CIMIT will use media visibility as a tool to communicate its core messages and influence a wide range of audiences, including donors, industry, and the public. Milestone events and accomplishments will serve as opportunities to tell the larger story of CIMIT.

CIMIT Academic Program: A core part of CIMIT's mission is the education of the next generation of researchers in the field of minimally invasive therapy. CIMIT is a place where engineers, physicians, and educators work side-by-side on innovative approaches to clinical problems. The next generation of researchers will need to be skilled in the development and implementation of new devices and procedures. They will need to be trained in the science of biomedical engineering, including the development of

new devices and therapeutic approaches, visualization techniques, models of anatomy, and real-time information processing. And they will need to understand the science of learning, including the development of new assessment strategies, as well as new tools, techniques, and theories of learning.

To help develop these skills, CIMIT is developing a course of study in the field of minimally invasive therapy research and practice, as well as a mentor program, where students and post-doctoral fellows participate in ongoing research projects.

Although a complete academic program is not expected to be up and running within the next academic or fiscal year, the intent is to develop the administrative, logistical, and theoretical infrastructure to make such a program possible. In particular, there are plans to develop deeper collaboration with the Health Sciences and Technology Program at MIT — as well as other departments within the university — and with the Harvard schools of Medicine, Education, Design, and Engineering.

CIMIT Training: CIMIT is committed not only to the development of new technologies, but also to their successful implementation and use in improving patient care. To this end, the training and assessment component of the CIMIT education program has three goals:

1. The development of evaluation programs, education and training programs, and performance assessments or certification programs for existing technologies
2. The development of such programs for technologies under development — including the design of specific technical features in new devices to support evaluation, training, and assessment
3. The development of new technologies specifically for education, training, and assessment

In conjunction with Mitsubishi Electric, CIMIT has been developing an interventional cardiology simulation that represents not only an enormous advance in simulator technology, but also incorporates an innovative "learning system" for interventional cardiology. The system includes a technical simulation of cardiac catheterization, a curriculum of standardized "patients," enhanced clinical features for training and assessment, and multi-media links to clinical and other supporting information. This technical and pedagogical system is designed to support the development of new devices and procedures, training and evaluation of cardiology fellows, and continuing medical education for practicing cardiologists. Specific technical features of the simulator, such as an annotated logbook, were designed with specific pedagogical goals in mind.

A team of technical, clinical, and educational experts to develop leading-edge techniques and technologies for simulation-based training and assessment is in the process of being assembled to achieve these goals.

Appendix B: List of Personnel Receiving Pay

PROJECT TITLE	NAME	TITLE/ROLE	
CARDIOVASCULAR	Muller, James, M.D.	Cardiovascular Program Team Leader	
OCT for plaque characterization	Bouma, Brett E, Ph.D.	Principal Investigator	
	Jang, Ik-Kyung, M.D. Ph.D.	Investigator	
	Brady, Thomas, M.D.	Investigator	
	Shishkov, Milen, Ph.D.	Research Fellow	
	Tearney, Gary, M.D. Ph.D.	Investigator	
	Aretz, Thomas, M.D.	Investigator	
	Houser, Stuart, M.D.	Investigator	
Minimally invasive cardiac surgery	Torchiana, David, F, M.D.	Principal Investigator	
	Jang, Ik-Kyung, M.D. Ph.D.	Co-Investigator	
	White, Jennifer, M.D.	Research Fellow	
	Titus, James	Lab Supervisor	
Endothelial activation mkrs - CVD	Gimbrone, Michael A, M.D.	Principal Investigator	Subcontract BWH
CANCER	Tanabe, Kenneth, M.D.	Cancer Program Team Leader	
Focused ultrasound- treatment of breast cancer	Jolesz, Ferenc. M.D.	Principal Investigator	Subcontract BWH
NIR spectroscopy-Barrett's esophagus	Nishioka, Norman, M.D.	Principal Investigator	
	Schomacker, Kevin, Ph.D.	Co-Investigator	
	Brand, Stephan, M.D.	Research Fellow	
	Puricelli, William, R.N.	Clinical Coordinator	
OCT imaging of esophageal lessions	Nishioka, Norman, M.D.	Principal Investigator	
	Bouma, Brett, Ph.D.	Co-Investigator	
	Asimellis, George, Ph.D.	Research Fellow	
	Puricelli, William, R.N.	Clinical Coordinator	
Precancerous diagnostics	Perelman, Lev T., Ph.D.	Principal Investigator	Subcontract MIT
STROKE	Koroshetz, Walter, M.D.	Stroke Program Team Leader	
	Gonzalez, R, Gilberto M.D. Ph.D.	Stroke Program Team Leader	
Assessment neoroprotective brain cooling	Sorensen, Alma Gregory, M.D.	Principal Investigator	
	Koroshetz, Walter, M.D.	Co-Investigator	
	Lee, Albert, M.D.	Research Scientist	
Laser thrombolysis of clot	Gonzalez, R, Gilberto M.D. Ph.D.	Principal Investigator	
	Putman, Christopher, M.D.	Investigator	
	Norbash, Alexander, M.D.	Investigator	
	Budzik, Ronald, M.D.	Investigator	
	Maynard, Kenneth, Ph.D.	Investigator	
Diffusion optical tomography brain hemmorhage	Boas, David, M.D.	Principal Investigator	
	Koroshetz, Walter, M.D.	Co-Investigator	
	Sorensen, Alma Gregory, M.D.	Investigator	
	O'Donnel, Joan, R.N.	Nurse Coordinator	
	Gaudette, Thomas, Ph.D.	Engineer	
Use proton beam rad - intract epilepsy	Brissman, Jonthan, L., M.D.	Principal Investigator	
Measure CV reactivity- functional MRI	Greenberg, Steven, M, M.D. Ph.D.	Principal Investigator	
	Mckenzie, Sarah, B.A.	Research Assistant	
TRAUMA			
Real time Dx of CNS trauma	Ling, Jeffrey, M.D.	Principal Investigator	Subcontract HMJF
NIR of tissue pH & O2 in ischemia	Puyana, Jaun Carlos, M.D.	Principal Investigator	Subcontract BWH
Improved tactile sensations	Kerrigan, D. Casey, M.D.	Principal Investigator	Subcontract SRH
Hepatic functions monitor	Puyana, Juan Carlos, M.D.	Co-Investigator	Subcontract HMC
NEW INITIATIVES			
Chemical assay (pH, O2, etc.)	Cunningham, Brian, Ph.D.	Principal Investigator	Subcontract DL
Lung volume reduction	Ingenito, Edward, M.D. Ph.D.	Principal Investigator	Subcontract BWH
Simulation: meas & display haptic prop for Surg	Salisbury, Kenneth, Ph.D.	Principal Investigator	Subcontract MIT
Simulation	Banach, Timothy, M.S.	Principal Investigator	Subcontract DL
Computer based distraction device	Kaban, Leonard B, D.M.D., M.D.	Principal Investigator	
	Glowacki, Julie, Ph.D.	Investigator	
	Seldin, Edward B, D.M.D., M.D.	Investigator	
	Troulis, Maria, J, D.D.S.	Investigator	
	Emanuel, David, D.D.S. M.D.	Investigator	
	Kikinis, Ronald, M.D.	Investigator	
Transderm drug delivery	Weaver, James C, Ph.D.	Principal Investigator	Subcontract MIT

ADV TECHNOLOGY TEAMS	Pien, Homer, Ph.D.	ATT Program Team Leader	Subcontract DL
	Brady, Jean	Project Manager	Subcontract DL
	Vacanti, Joseph, M.D.	ATT Program Team Leader	
	Oesterle, Steven M.D.	ATT Program Team Leader	
Biomaterials	Langer, Robert, Ph.D.	Principal Investigator	Subcontract MIT
Surgical Planning	Westin, Carl-Frederick, Ph.D.	Principal Investigator	Subcontract BWH
Realtime Ultrasound - IGTx	Grimson, Eric, Ph.D.	Principal Investigator-MIT	
Tissue engineering	Vacanti, Joseph, M.D.	Principal Investigator	
	Anderson, Rox, M.D.	Investigator	
	Kaihara, Satoshi	Surgical Fellow	
	Solan, Lalan	Research Technician	
NEW PROGRAMS			
CIMIT Clinical Programs	Rattner, David, M.D.	Clinical Programs Director	
	Gesner, Charlotte	Admin Assistant	
CIMIT Education Program	Shaffer, David, Ph.D.	Co-Director	
	Weissbach, Karen	Program Specialist	
Technology Assessesment Program	Gazelle, Scott G., Ph.D.	Principal Investigator	
	McNaughton-Collins, Mary, M.D.	Outcomes Analyst	
	Halpern, Elkan F., Ph.D.	Statistician	
	Gleason, Suzanne, Ph.D.	Economist	
	Lester, Jessica, M.M.	Research Associate	
	Mcmann, Pamela, B.S.	Research Associate	
CIMIT Strategy	Parrish, John A., M.D.	CIMIT Director	
	Nolan, Marybeth	Admin Assistant	
	Shulman, Beth	Secretary	
CIMIT Leadership	Brady, Thomas, M.D.	Associate Director	
	Ryan, Jeanne	Admin Assistant	
CIMIT Scientific Leadership	Anderson, Rox, M.D.	Scientist	
	Jang, Ik-Kung, M.D. Ph.D.	Scientist	
	Nishioka, Norman, M.D.	Reserach Awards Program Director	
	Cohen, Melissa	Admin Assistant	
	Isaacson, Keith, M.D.	Industry Medical Liaison	
	Stiller, Jane	Admin Assistant	
	Deutsch, Thomas, Ph.D.	Scientist	
CIMIT Operations	Osborn, Lynn, R	Director of Admin and Finance	
	Garber, Kelly	Admin Assistant-term	
	Herry-Galloway, Michelle	Admin Assistant-term	
	Robichaud, Annette	Finance Director	
	Cho, Unsuk	IS Manager	
	Greaves, Kenneth	IS Manager-term	
	Mitchell, Lisa	IS Director	Subcontract DL
	Taylor, George	Courier	
CIMIT Progran Development	Kigin, Colleen	Director of Program Development	
	Palumbo, Andrea	Clinical Studies Coordinator-term	
	Schlendorff, Kelly	Clinical Studies Coordinator	
	McAuliffe, Daniel	Stroke Program Manager	
	Strod, Deborah	Technology Associate	
CIMIT Business Develoment	Crosby, Janice	Director Business Development	
	Humphrey, Ann	Industry Account Manager	
	Carpenter, Janine	Industry Project Coordinator	
	Smith, John J., M.D.. J.D.	FDA Program Director	

Legend:

BWH = The Brigham and Women's Hospital, Inc.
DL = The Charles Stark Draper Laboratory, Inc.
HMC = The Harvey Mudd College
HMJF = The Henry M. Jackson Foundation
MIT = The Massachusetts Institute of Technology
SRH = The Spaulding Rehabilitation Hospital
"term" = Terminated - no longer working for Program

Appendix C: Graduate Degrees Resulting from Award Support

There are no fellows or students who will receive a graduate degree as a result of award support.